Thesis for doctoral degree (Ph.D.)
2019

Causal effects of education on cognition – How do we generate evidence?

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Stockholm 2019

Published by Karolinska Institutet.
Illustrations: Seblova, Dominika.
Printed by Eprint AB, 2019.

ISBN 978-91-7831-380-8

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Public defense: Friday 22nd March 2019 | 9:30 AM | CMB hall – Berzelius Väg 21, Solna | Karolinska Institutet, Sweden

To my mum

To my grandmothers – biological and adoptive

To all those interested

SCIENTIFIC ABSTRACT

Background: Education is a key institution in our societies, and should prepare us for future by improving cognition and teaching us needed life skills. Education is associated with many aspects of life, including health. For example, there is hope that improved education may help to reduce the burden of dementia, which is a large public health challenge for which treatment is missing. However, such hopes assume causality of the relationship between education and dementia.

Aim: The primary aim of this doctoral thesis was to examine the relationship between formal education and cognition (i.e. early-life cognition, cognitive decline and neuropathological disturbances to cognition in form of dementia) during the life-course. The secondary aim was to discuss how we can generate evidence on causal relationships and infer causation in epidemiology.

Methods: This thesis adopted a plurality and triangulation of evidence approach with regards to arriving at causal conclusions. The individual studies employed diverse designs in the exploration of links between education, cognition and dementia. Study I described thirty-year trends in the burden of dementia in inpatient records according to educational level. In Study II, we exploited a quasi-experimental comprehensive school reform in order to ascertain causal relationship between education and intelligence in men at military conscription. Further, we explored the heterogeneity of the effect according to childhood socioeconomic position. Study III focused on dementia. In order to investigate the causal effect of education on dementia diagnosis in Swedish registers, we used a primary schooling reform as a natural experiment. The reform had minimal spill-over effects on adult socioeconomic factors. The last study (Study IV) was a systematic review and meta-analysis summarizing the evidence from population-based studies of healthy adults. It examined the association between education and change in episodic memory, a cognitive domain with strong links to dementia.

Results: The burden of dementia in Swedish inpatient records began to decline during the last half a decade. Educational inequalities in dementia incidence remained stable and those with the highest educational attainment had the lowest dementia incidence rates. The comprehensive school reform increased intelligence and reduced socioeconomic disparities in cognition. However, in Study III we did not discover any substantial effect of the primary schooling reform on dementia risk. Similarly, the meta-analytic estimate indicated that the association between education and age-related decline in episodic memory is negligible.

Conclusions: Education is associated with level of cognition, but not decline - at least not in the episodic memory domain. Further, prolonged education cannot be uncritically assumed to reduce dementia burden, especially in absence of spillover effects to adult socioeconomic factors. However, education fulfils one of its many aims by increasing early-life cognition, and also has the potential to reduce socioeconomic inequalities in cognitive ability.

POPULAR SCIENCE SUMMARY: DOES EDUCATION IMPROVE COGNITIVE HEALTH?

We attend school for many years of our life believing that it will make us smarter and prepare us for the future by teaching us needed life skills. Research also shows that longer education improves survival and some health outcomes. Thus, there is hope that longer education may improve cognitive abilities and also help to reduce the burden of dementia, which is increasing worldwide.

In order to see if education may have these effects, this doctoral thesis examined the relationship between education and cognitive abilities during life. We studied intelligence in adolescence, cognitive decline in mid- and old-age and occurrence of dementia. Dementia is related to cognition because person's ability to think, remember events, reason, and manage his/her own life continually declines due to different underlying diseases. The first study in this thesis, described the developments in burden of dementia in Sweden. We calculated how many men and women with different levels of education received dementia diagnosis at Swedish hospitals during a 30-year period (1987-2016). The number of people with dementia diagnosis was the lowest among those with some university education; and the highest among those with only compulsory schooling.

Yet, this does not say that higher education truly protects against dementia. Studying education is complicated because people do not choose their schooling randomly. Our families, friends, income, availability of schools, and other factors influence what and for how long we study. Therefore, isolating the effect of education on cognition from the effect of these other factors is hard. To assess if one factor really causes an outcome, researchers normally conduct randomized experiments. Yet, because of education's importance for our lives, researchers cannot randomize individuals to education – in other words they cannot decide for how long each person should study and then observe their outcomes.

One alternative is to take advantage of historical events, such as schooling reforms, because they may act at random and thus mimic a randomized experiment. In the second study we used this approach and exploited Swedish school reform ("Enhetskolereformen") that prolonged compulsory education from 8 to 9 years. We found that prolonging education increased IQ scores in men at military conscription. Further, the reform helped those from the poorest segments of society the most. Thus, it reduced socioeconomic disparities in intelligence. Our third study used a different school reform ("Folkskolareformen") that prolonged primary schooling from 6 to 7 years. In this study, we found that higher education did not substantially decrease dementia occurrence. The final (fourth) study summarized existing evidence on the association of education with change in one type of memory, so called episodic memory, in healthy adults. Episodic memory is cognitive function linked to dementia and perceived quality of life in older age. The fourth study indicated that the association between education and change in memory during aging is small.

Overall, education is associated with level of cognitive abilities. Nevertheless, prolonged education does not slow decline in episodic memory. Further, our findings indicated that education cannot always be assumed to reduce the burden of dementia. However, this thesis showed that education positively influences early-life cognition, and has the potential to reduce socioeconomic disparities. Education without a doubt remains an important pillar of our societies with positive effect on health and has the potential to improve health equity.

VŠEOBECNÉ SHNUTÍ: MÁ VZDĚLÁNÍ POZITIVNÍ VLIV NA KOGNITIVNÍ ZDRAVÍ?

Strávíme léta života školní docházkou v naději, že budeme chytřejší, připravenější na život a že získáme potřebné dovednosti. Závěry vědců ukazují, že delší doba školní docházky prodlužuje délku života a má pozitivní vliv na určité aspekty zdravotního stavu. Někteří též doufají, že delší školní docházka zlepší kognitivní schopnosti a tak snad přispěje ke snížení výskytu demence, který je zatím celosvětově na vzestupu.

Abychom zjistili, zda vzdělání má skutečně na výskyt demence vliv, zkoumá tato dizertační práce vztah mezi prodlouženým vzděláváním a kognitivními schopnostmi během celého života. Zaměřili jsme se na inteligenci v ranné dospělosti, úbytek kognitivních schopností ve středním a seniorském věku a na výskyt demence. Demence a kognitivní schopnosti spolu souvisí – kvůli degenerativním procesům, které provázejí onemocnění demencí, dochází k postupné ztrátě paměti, schopnosti uvažovat a zvládat běžné životní úkony. První studie v této dizertační práci popisuje vývoj výkytu demence ve Švédsku. Spočítali jsme, kolika mužům a ženám s různou úrovní nejvyššího dosaženého vzdělání byla v nemocnicích ve Švédsku během období 30ti let (1987–2016) diagnostikována demence. Nejnižší počet lidí s diagnózou demence byl mezi univerzitně vzdělanými a nejvyšší u osob jen se základním vzděláním.

To však neznamená, že vyšší vzdělání skutečně před demencí chrání. Výzkum vlivů vzdělávání je komplikovaný, neboť lidé si obor ani délku vzdělávání nevybírají náhodně. Na to, jak dlouho a co člověk studuje, má vliv rodina, přátelé, majetek, dostupnost škol a mnoho dalších faktorů. Proto je obtížné zjistit, do jaké míry jsou kognitivní schopnosti ovlivněny vzděláním a jaký je podíl dalších faktorů. K posouzení vlivu jednoho faktoru na určitý výsledek provádějí vědci randomizované studie. Vzdělání je však pro náš život příliš důležité, aby bylo možné jedince do určitého typu vzdělání randomizovat – jinými slovy, vědci nesmějí rozhodovat, jak dlouho a co bude jednotlivec studovat jen kvůli vědeckému zkoumání.

Jedna z možností, jak zkoumat vliv vzdělávání na zdravotní stav, je využít skutečných historických událostí, např. vzdělávacích reforem, které plošně změnily délku vzdělávání, aniž by se dotkly ostatních faktorů. Takové reformy se přibližují randomizovaným studiím. Toho jsme využili ve druhé studii dizertační práce a zkoumali jsme švédskou školní reformu (“Enhetskolereformen”), která prodloužila povinné vzdělání z 8 na 9 let. Zjistili jsme, že muži při odvodu do armády měli vyšší IQ, pokud absolvovali devítiletou školní docházku. Dále jsme zjistili, že z této reformy nejvíce těžili muži z nejchudších vrstev společnosti, čímž došlo ke snížení socioekonomických nerovnostích v inteligenci. Třetí studie se zaměřila na jinou školní reformu (“Folkskolareformen”), která prodloužila nižší stupeň povinného vzdělávání ze 6 na 7 let. Zjistili jsme, že delší vzdělání nijak zásadně nesnížilo výskyt demence. Čtvrtá studie shrnula současné výsledky týkající se vztahu mezi vzděláním a změnou v jednon z typů paměti (epizodické) u zdravých dospělých osob. Epizodická pamět je důležitá pro subjektivní hodnocení životní kvality a její výrazný pokles je typickým příznakem demence. Nalezli jsme jen malý vztah mezi délkou vzdělání a změnami paměti během procesu stárnutí.

Pokud shrneme naše zjištění, vzdělání s kognitivními schopnostmi souvisí, delší školní docházka však nezpomaluje pokles paměti během stárnutí s normálním průběhem a ne vždy snižuje výskyt demence. Nicméně delší školní docházka zvyšuje inteligenci v dospívání a může snížit socioekonomické nerovnosti. Vzdělávání tak bezpochyby zůstává v moderní společnosti důležitou institucí schopnou pozitivně ovlivnit zdraví jednince a současně snížit nerovnosti v oblasti zdraví.

POPULÄRVETENSKAPLIG SAMMANFATTNING: LEDER UTBILDNING TILL BÄTTRE KOGNITIV HÄLSA?

Vi ägnar en betydande del av våra liv åt skolan, i förhoppningen om att det ska göra oss smartare och förbereda oss inför framtiden genom att ge oss kunskaper och förmågor. Forskning visar att utbildning är förknippat med ett längre liv och bättre hälsa. Det finns dessutom en förhoppning om att utbildning kan förbättra kognitionen och minska risken för demens, som idag utgör ett växande globalt problem.

För att undersöka om utbildning verkligen har dessa effekter analyserade vi sambanden mellan utbildning och kognition i olika faser av livet. Vi studerade intelligens bland ungdomar, kognitiva nedsättningar bland vuxna och äldre personer samt förekomsten av demenssjukdomar. Demens är nära kopplat till kognition, eftersom förmågan att tänka, komma ihåg händelser, resonera och att ta hand om sig själv avtar fortlöpande hos den som drabbats av en demenssjukdom. I avhandlingens första studie beskrivs hur förekomsten av demens har utvecklats över tid i Sverige. Vi uppskattade riskerna att få en demensdiagnos vid ett svenskt sjukhus under en 30-årsperiod (1987-2016) för kvinnor och män med olika utbildningsnivåer. Sannolikheten att få en demensdiagnos var lägst bland de som hade en universitetsutbildning och högst bland de som endast hade en grundskoleutbildning.

Detta innebär dock inte nödvändigtvis att utbildning skyddar mot demens. Det är komplicerat att studera utbildning, eftersom olika utbildningar inte är slumpmässigt fördelade i befolkningen. Familjebakgrund, vänner, inkomst, tillgängligheten av skolor och en rad andra faktorer påverkar vad och hur länge vi studerar. Detta gör det svårt att skilja effekten av utbildning från effekterna av övriga faktorer. Experiment utgör den mest effektiva metoden för att studera orsakssamband. Men av etiska och praktiska skäl är det inte möjligt att experimentera med utbildningsnivåer - det vill säga, bestämma vad och hur länge olika personer ska studera för att sedan observera eventuella effekter.

En alternativ strategi är att dra nytta av historiska händelser, som till exempel skolreformer. De liknar experiment i det att de inneburit förändringar i utbildningen för vissa, men inte för andra. I den andra studien använder vi denna strategi och utgår från den svenska Enhetskolereformen som förlängde grundskolan från 8 till 9 år. Vid mönstringen hade de män som fick den förlängda utbildningen högre IQ, dessutom var denna ökning störst bland de som kom från samhällets fattigaste skikt. Alltså minskade reformen de socioekonomiska skillnaderna i intelligens. I den tredje studien använde vi oss av en tidigare skolreform (Folkskolereformen”), som förlängde grundskolan från 6 till 7 år. Vi fann att den förlängda utbildningen inte ledde till någon betydande förändring i risken för demens. I avhandlingens sista studie sammanfattade vi kunskapsläget om sambandet mellan utbildning och förändringar i en specifik kognitiv funktion (episodiskt minne) bland friska vuxna. Det episodiska minnet är en förmåga som är kopplad till demens och den subjektiva hälsokvalitén bland äldre. Resultatet visade att sambandet mellan utbildning och åldersbundna förändringar i det episodiska minnet under åldrandet är svagt.

Sammanfattningsvis finns det ett samband mellan utbildning och de kognitiva förmågorna. Men en längre utbildning bromsar inte den åldersbundna försämringen av det episodiska minnet. Dessutom visar vi att en längre utbildning inte alltid leder till en minskad risk för demens. Däremot kan en längre utbildning ha en positiv effekt på kognitionen tidigt i livet samt kan bidra till att minska socioekonomiska skillnader. Utbildning är utan tvekan en central institution i dagens samhälle som bidrar till en bättre hälsa och som har potential att minska hälsoskillnaderna mellan olika sociala grupper.

LIST OF SCIENTIFIC PAPERS

This thesis is based on four scientific articles, to which we refer by their Roman numbers throughout the text. The published papers are reprinted with the permission of the publisher.

I. **Seblova, D.**, Quiroga, M.L., Fors, S., Johnell, K., Lövdén, M., de Leon, A.P., Svensson, A.C., Wicks, S. and Lager, A., 2018. Thirty-year trends in dementia: a nationwide population study of Swedish inpatient records. *Clinical Epidemiology,* 10, p.1679-1692

II. Lager, A., **Seblova, D.**, Falkstedt, D. and Lövdén, M., 2016. Cognitive and emotional outcomes after prolonged education: a quasi-experiment on 320,182 Swedish boys. *International Journal of Epidemiology*, 46 (1), pp.303-311

III. **Seblova, D.**, Fischer, M., Fors, S., Johnell, K., Karlsson, M., Nilsson, T., Svensson, A.C., Lövdén, M., Lager, A., 2019. Is there a direct causal effect of education on dementia? A Swedish natural experiment on 1.3 million individuals. *Submitted*

IV. **Seblova, D.**, Berggren, R., Lövdén, M., 2019. Education and age-related decline in episodic memory performance: systematic review and meta-analysis of longitudinal studies. *Manuscript*

CONTENTS

LIST OF ABBREVIATIONS

ACT	Anatomical Therapeutic and Chemical codes
AD	Alzheimer's Disease
CI	Confidence Interval
CDR	Cause of Death Register
CT	Computed Tomography
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
ICD	International Classification of Diseases
IQ	Intelligence Quotient
ISCED	International Standard Classification of Education
LISA	Longitudinal Integration Database for Health Insurance and Labour Market Studies
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
NIPR	National Inpatient Register
OCEBM	Oxford Centre for Evidence-Based Medicine
RTC	Randomized Control Trial
SE	Standard Error
SEP	Socioeconomic Position
SD	Standard Deviation
SNP	Single-Nucleotide Polymorphism
TICS	Telephone Interview of Cognitive Status
VAD	Vascular Dementia

1 INTRODUCTION

1.1 HOW TO GENERATE EVIDENCE ON CAUSATION?

Epidemiology has always been concerned with informing on causal relationships, and diverse criteria, such as the Bradford Hill ones (Hill 1965), were developed over time. Yet, studying causal relationships was not the sole purpose of the field. Nowadays, there is an ongoing debate regarding the "elevation of causal studies as the science of epidemiology" (Ebrahim, Ferrie & Davey Smith 2016). Some prominent figures in epidemiology seem to support the superiority of causal studies. For example, Rothman, Gallacher and Hatch write that:

> *"Surveys of opinions, of the prevalence of disease, of habits or of environmental exposures may be informative, but they are not science in the same way that causal studies about how nature operates are science." (2013, p. 1013, emphasis added).*

In response, a number of authors pointed out the need for pluralism of evidence and subsequent triangulation (Krieger & Davey-Smith 2016; Vandenbroucke, Broadbent & Pearce 2016). Using historical examples, such as smoking, these commentaries advocated that a single study, which in and of itself provides a poor evidence for a causal relationship, may supply instrumental information when the whole of available evidence is considered (Krieger & Davey-Smith 2016). Subsequently, one poor quality (from a causal point of view) study may still be crucial for the progress of science. On the other hand, even experimental evidence can leave causal questions unsettled, as long as the findings do not rule out all alternative hypotheses (Krieger & Davey-Smith 2016). Overall, this thesis aligned itself with the pluralistic approach and employed diverse study designs in its examination of the relationship between formal education, cognition and dementia during the life-course.

Nevertheless, we believe that one central distinction needs to be made and that is the distinction between *making causal statements* versus *arriving at causal conclusions*. Some methodologies or study designs, such as randomized control trials (RCTs) or quasi-experiments, are more appropriate for examining causal relationships (Shadish, Cook & Campbell 2002) and thus allow for *making causal statements* with higher confidence. That in our view does not mean that they confirm causality and thus *arrive at a causal conclusion*. We maintain that individual studies can get us closer to understanding the causal nature of a relationship. Yet, as Vandenbroucke, Boadbent and Pearce (2016) write "the important causal questions are asked not within studies, but between them." (p.1785). Similarly, we believe that we arrive at causal conclusions across different studies, and that the key epidemiological challenge is to use "different kinds of evidence to arrive at one overall verdict" (Vandenbroucke, Boadbent & Pearce 2016, p. 1783). To set the scene for questions posed in this thesis, the rest of the introduction covers the key available evidence and the "in between" questions or, in other words, the gaps in knowledge with regards to the relationship between education, cognition and dementia.

1.2 EDUCATION

The educational system is a key institution in our contemporary societies. Governments are tasked to provide education for everyone, and citizens are required by law to attend schooling for a certain amount of time. In 2016, governments across the globe invested on average 14.0% of their governmental budget in education (range 0.8% to 42.8%) (World Bank Group 2018). Such levels of investments highlight the importance placed on education by our societies. Ideally, education should fulfil many purposes. For example, it should prepare individuals for their life by advancing their factual knowledge, as well as cognitive and socio-emotional skills. Furthermore, education also affects other aspects of life, such as health (Feinstein et al 2006; Galama, Lleras-Muney & Kippersluis 2018). In summary, education is important to many facets of our lives and thus has been studied in diverse scientific fields, such as economics and social epidemiology. Nevertheless, gaps in our knowledge remain.

1.2.1 Multiple attributes of education as a variable

Studying education's effect on outcomes is complicated by the fact that it is a bundled process (Glymour, Avendano, & Kawachi 2014, p.36). In other words, education has many attributes that may influence the studied outcomes. Thus operationalization of the educational variable is not as straightforward as it may seem at first. The most common operationalization of education in research is the addition of one more year of formal education. Such approach considers change from for example 0 to 3 years equivalent to change from 9 to 12 years. Yet, the content, form and quality of education at different levels vary and may impact estimation of education's effects. Furthermore, historically and geographically the length of a school year has differed. An extreme example comes from the United States where prior to legally mandated desegregation minimum term lengths were 50 to 100% higher for white children than black. Subsequently, a black child could have 2.5 years lower time truly spent in education than a white child born in the same year, same state, and who attended school for the same number of years (Glymour & Manly 2008). In addition, there are likely substantial differences in attendance rates, magnifying the inequalities in educational attainment. Education may also differ in many other aspects such as quality, timing of education, class size, or class social composition (Rehkopf, Glymour & Osypuk, 2016). Each of these aspects may influence studied outcomes. For example, the social composition of class may define the learning environment but also one's future social capital. Furthermore, there are also degree effects, i.e. benefits of obtaining a formal qualification, such as access to further education, better job opportunities and effects on other midlife socioeconomic factors. Thus, there is a myriad of plausible mechanisms linking education and health and the evidence regarding the mechanisms is weak (Feinstein et al 2006; Rehkopf, Glymour & Osypuk, 2016). In summary, when interpreting

the association between education and outcome of interest, it is essential to understand the context (geographical, historical, etc.) and what changes higher educational achievement could bring about in individual's life.

1.2.2 Studying education as a cause

There is a large interest in determining if education causes better health, due to presence of robust associations between education and many health outcomes (Feinstein et al 2006; Galama, Lleras-Muney & Kippersluis 2018). A majority of the evidence regarding this topic comes from observational studies, where education is not manipulated by researchers. In such setting, inference rests on an assumption that there are no unmeasured mutual causes of education and the studied health outcome. Yet, there are many possible common causes. Probably the most important factor that is related to both education and health is early-life intelligence. Those with higher early-life intelligence likely proceed further in the educational system. Later in life, they presumably reap the benefits, such as higher paying jobs, better access to healthcare and others. Failing to take early-life intelligence into account would confound (i.e. bias) the relationship between education and later life health outcomes. Other examples of common causes are childhood health or socioeconomic position, since they can also influence educational achievement and later life health. Experiments with random assignment are used to avoid confounding (Shadish, Cook & Campbell 2002). Thanks to randomization, the distribution of possible confounders is on average the same between exposed and unexposed. Subsequently, an estimation of causal effect is more straightforward.

Randomizing individuals to the full range of possible educational careers is likely not possible, given the importance of education to our lives, length of educational careers and interest in life-long impacts. In the absence of randomized experiments, so-called natural- or quasi-experiments can be used for estimation of causal effect. In quasi-experiments, an intervention is deliberately introduced, but not randomized. In natural experimental settings, none controls the conditions. Instead, variation that comes from naturally occurring events, for example natural disasters or changes in policy, is used (Glymour 201; Shadish, Cook & Campbell 2002). In summary, these approaches may allow for examination of education as a cause if pseudo-randomization occurs. Therefore, we used such approaches in this thesis, alongside traditional observational analyses using formal education (length and highest degree achieved) as an exposure.

1.3 COGNITION AND DEMENTIA

Cognitive ability involves many domains, such as perception, attention, or memory. Thus, many individual psychometric tests aim to measure performance of a specific domain. Cognition is also frequently conceptualized as a general ability (g-factor), which captures the correlation among the individual domains (Warne & Burningham 2019). While cognitive performance declines with age, timing of the decline differs between the domains. Performance on processing aspects of cognition (e.g. psychomotor speed, or fluid reasoning) starts to decline already in middle age (Rönnlund & Nilsson 2006; Schaie 1994, 2005). On the other hand, crystallized intelligence performance, which is mainly based on acquired knowledge, declines at later ages (Rönnlund et al. 2005; Schaie 1994, 2005).

Cognitive ability is a natural antecedent of dementia - a cognitive decline beyond a threshold of cognitive functioning. Yet, it is likely that dementia has a partly unique etiology from other forms of cognitive aging. In brief, dementia is a syndrome defined by degenerative impairment of cognitive processes to the point of interference with activities of daily living (Livingston et al 2017), such as managing money, preparing meals, bathing or dressing. A timing of dementia onset (threshold surpassing) may differ due to variation in baseline levels of cognitive ability if rates of decline are parallel. Cognitive ability substantially varies between individuals. The variability is correlated to age (Deary, Pattie & Starr 2013) and some studies reported increased variability in old-age cognition (de Frias et al. 2007). Theoretically, those with initially higher level of cognitive performance reach cognitive impairment threshold later life. Alternatively, the rates and shapes of cognitive decline might also vary across individuals (Yu et al 2012). Thus, dementia incidence in old age may be affected by differences in the level and/or the rate and shape of decline in cognitive performance.

1.3.1 Studying dementia

"Dementia is the greatest global challenge for health and social care in the 21st century" according to the Lancet Commission on Dementia Prevention, Intervention and Care (Livingston et al 2017, p. 2673). There were approximately 47 million individuals living with dementia in 2015, and according to projections this number will nearly triple by 2050 (Prince et al 2015). Dementia is a severe condition, which brings about a gradual loss of basic abilities. Thus, eventually individuals with dementia become fully dependent on others, which places large demands on care provision by family and public sector. For example, the annual cost of dementia worldwide reached $818 billion, and majority of the costs (85%) were attributed to family and social care (Livingston et al 2017). Overall, there is a tremendous interest in studying dementia and in finding functioning preventative strategies and treatment. Yet, at this time there is no cure, and only symptomatic treatment is available.

Etiology of dementia and the underlying neuropathologies are still poorly understood. Typically, the term dementia

encompasses a range of neurological disorders and is used as an umbrella term for them throughout this thesis. Each of the neurological disorders has specific characteristics. Alzheimer's disease (AD) dementia accounts for 50 to 70% of all cases (Winblad et al 2016), and gradual memory loss is its characteristic. The hallmarks of the AD neuropathology are changes in tau-tangles and beta-amyloid. However, the Alzheimer's disease neuropathology can be confirmed only by autopsy. Vascular dementia (VAD), which frequently presents with rapid decline in cognitive abilities after strokes and microvascular infarcts, or mixed pathology dementia, are the second most common types (Livingston et al 2017). Yet, there are still other types, such as Lewy bodies or Frontotemporal dementia.

Diagnosing dementia clinically and for research purposes is complicated by the diversity of the disorders, the fact that the neurodegenerative processes likely begin many years prior to diagnosis (Rajan et al 2015) and by our limited understanding of the neuropathology. If certain signs and symptoms are present, and unexplained by other causes, then dementia diagnosis is assigned. Thus, it is a diagnosis of exclusion (Devere 2016). The ideal clinical workup is a complex examination, which includes comprehensive physical and neuropsychological tests, and proxy interviews with relatives. Sometimes the examination also encompasses brain imaging, such as structural magnetic resonance imaging (MRI) or computed tomography (CT) scans. Finally, current movement towards biomarker-based diagnosis, especially AD, further muddies the issue (e.g. Hudd et al 2019).

In research, a gold standard for dementia diagnosis is lacking (Weuve et al 2015), and thus assessing validity of the dementia outcome across data sources is difficult. Nevertheless, in population-based studies protocols for assigning dementia diagnosis can be kept constant, which is an advantage especially when studying disease prevalence or incidence. On the whole, population-based studies differ substantially in their procedures for assigning dementia diagnosis. Some studies adopted the complex examination described above, and diagnosis was assigned by a team of physicians with diverse specialties. Other studies included less extensive diagnostic work-up. For example, they based their diagnoses predominantly on shorter cognitive assessments, such as the Mini Mental State Examination (MMSE) or Telephone Interview of Cognitive Status (TICS). And some population-based studies used only self-reported measures of dementia, which likely have poor quality, especially in patients with severe dementia. Yet, diagnoses from population-based studies are the pragmatic gold standard, when assessing validity of dementia in "secondary-level of evidence" studies which use healthcare data linkage to identify dementia cases.

1.4 LINKS BETWEEN EDUCATION, COGNITION AND DEMENTIA

Cognitive ability is partly heritable, but it is also shaped by one's environment (Protzko 2015). For example, formal education is associated with cognitive performance. Yet, the relationship is likely bidirectional. In other words, those with higher inherited ability are more likely to go further in the educational system and the education one receives impacts one´s cognitive ability. A meta-analysis found a 0.48 correlation between early-life intelligence and later educational achievement (Strenze 2007). Thus, there is a potential for bias by early-life intelligence when examining education in observational setting. Nevertheless, according to a review by Ceci (1991), quantity of schooling causally affects IQ scores, a typical measure of general cognitive ability. Other studies using school reforms also indicated a causal relationship between education and intelligence (Brinch & Galloway 2012; Carlsson et al 2012; Cliffordson & Gustafsson 2001).

When educational achievement was examined in relation to old-age cognition (60+) a positive association was found in concerning the level of cognitive abilities in healthy older adults (Opdebeeck, Martyr & Clare 2016). Even this relationship seems to be causal. A systematic review of quasi-experimental studies based on educational reforms (Table 1) indicated a positive effect of education on level of mid- to late-life cognition (Hamad et al 2018). Education's role for change in cognitive abilities throughout life has also been examined (Anstey & Christensen 2000; Lenehan et al 2014; Valenzuela & Sachdev 2006). Nevertheless, no consensus regarding education's role in relation to change in cognitive abilities has been reached.

In light of the relationship between education and cognitive ability in healthy individuals, it is not surprising that a large body of studies examined education in relation to dementia (Caamaño-Isorna et al 2006; Valenzuela & Sachdev 2006; Sharp & Gatz 2011). With regards to dementia occurrence, systematic summaries of evidence report an inverse association between educational level and dementia (Caamaño-Isorna et al 2006; Valenzuela & Sachdev 2006, Sharp & Gatz 2011). For example, a dose-response meta-analysis concluded that every year increase in education was associated with a 7% lower dementia risk (Xu et al 2016). All in all, education has been identified as a major modifiable risk factor for dementia. However, this rests on the assumption that the association between education and dementia is causal, which remains to be confirmed.

Table 1. Summary of studies exploiting compulsory schooling reforms as quasi-experiments in order to examine causal effect of education (one year increase) on cognitive abilities in mid- to late-life (based on review by Hamad et al 2018).

Study	Setting	Studied cohorts	Method	Outcome measurment	Main results	Results uncertainty
Glymour et al (2008)	HRS (USA)	1901-1947	Multiple CSLs used as IV	Memory (word list recall)	0.34	95% CI: 0.11 to 0.57
				Modified TICS mental status	-0,06	95% CI: -0.37 to 0.26
Mazumder (2008)	SIPP (USA)	1901-1925	Multiple CSLs used as IV	Senility/dementia/ Alzheimer's disease	-0.0015	SE 0.0006
Banks & Mazzonna (2012)	ELSA (United Kingdom)	1923-1943	CLS change in dropout Age used as RD	Memory (immediate and delayed word recall)	Men: 0.434	SE 0.187; p< 0.05
					Women: 0.352	SE 0.193; p< 0.1
				Executive function (verbal fluency and letter cancellation)	Men: 0.371	SE 0.185; p< 0.05
					Women: 0.093	SE 0.21; p>0.1
Mazzonna (2012)	SHARE (Multiple European Countries)	1926-1956	Multiple CSLs used as IV	Memory (word recall)	0.195	SE 0.079, p<0.01
Mészáros (2013)	SHARE (Multiple European Countries)	1945-1961	Multiple CSLs used as IV	Memory (word recall)	0.0487	SE 0.154; NS
Crespo et al (2014)	SHARELIFE (Multiple European Countries)	1940-1953, 1927-1961, 1943-1956	Multiple CSLs used as IV	Memory (word recall)	0.1183	SE 0.0574; p<0.05
Mazzonna (2014)	SHARE (Multiple European Countries)	1929-1962	Multiple CSLs used as IV	Memory (word recall)	0.164	SE 0.053; p<0.01
Schneeweis et al. (2014)	SHARE (Multiple European Countries)	1939-1956	Multiple CSLs used as IV	Memory (immediate word recall)	0.144	SE 0.066; p<0.05
				Memory (delayed word recall)	0.171	SE 0.078; p<0.05
				Verbal fluency	-0.26	SE 0.322; p>0.05
				Numeracy	-0.013	SE 0.023; p>0.05
Nguyen et al (2016)	HRS (USA)	1900-1953	Multiple CSLs used as IV	Dementia probability risk score	-0.095	95% CI: -0.148 to -0.042

CSL= Compulsory schooling law change; IV= Instrumental Variable; RD= Regression Discontinuity; TICS=Telephone Interview for Cognitive Status; HRS= Health and Retirement Study; SIPP= U.S. Census Bureau's Survey of Income and Program Participation; ELSA= English Longitudinal Study of Ageing; SHARE/SHARELIFE= The Survey of Health, Ageing and Retirement in Europe; CI= Confidence interval; SE= Standard error; NS= Statistically non-significant, details not provided in the study

1.4.1 Potential mechanisms and life-course perspective

Understanding the underlying mechanisms is important for designing successful public health interventions. However, there are many possible mechanisms that may shape the associations between education, dementia, and cognition in healthy aging. Further, diverse aspects of education may act through different mechanistic pathways.

Cognitive ability affects individuals' life trajectories, health and life span (Batty et al 2007; Gottfredson & Deary 2004; Strenze 2007). For example, a systematic review with meta-analysis indicated that higher early life intelligence is associated with lower mortality later in life (Calvin, Deary & Fenton 2010). Many possible mechanisms can be behind this association. Cognitive ability may impact health due to its role in individuals' interactions with the external environment in a broad sense. For example, cognitive ability probably affects educational trajectories, occupation, work environment, lifestyle and healthcare utilization. Research showed that effects of intervention tend to diminish after its conclusion. For example, a meta-analysis of randomized control trials that increased IQ in childhood showed that the effects fade after conclusion of the intervention (Protzko 2015). Thus, if education is viewed as an intervention on cognitive ability, spill-over effects on adult socioeconomic factors may even be required in order to observe health improvements. There are also other possible mechanisms. For example, cognitive ability may affect intra-individual processes, such as recognition and modulation of somatic reactions, which subsequently may impact health (Fazekas, Leitner & Pieringer 2010; Gottfredson 2004).

Education might also influence dementia presence, onset and progress in various ways (Liu, Jones & Glymour 2010). Further, such relationships may differ from education's effect on normal cognitive aging since dementia might present unique pattern of cognitive decline. In Figure 1, we show some possible pathways between prolonged education and dementia incidence. For example, prolonging formal education may intervene on cognitive ability via cognitive stimulation. However, it may be difficult to distinguish between longer cognitive engagement or higher quality one, if prolonged education allows for more in depth learning. There are also many possible indirect pathways, which made be required in order to impact late-life outcomes, such as dementia.

Overall, cognitive ability, education and health are intertwined across the entire life course (Liu, Jones & Glymour 2010). Certain groups, or outcomes (disease onset vs. progression) may be affected only by specific mechanism. Thus, examining heterogeneous effects is key. Finally, individual studies need to be specific about the mechanistic pathways they are examining and which life-course model or models they may correspond to.

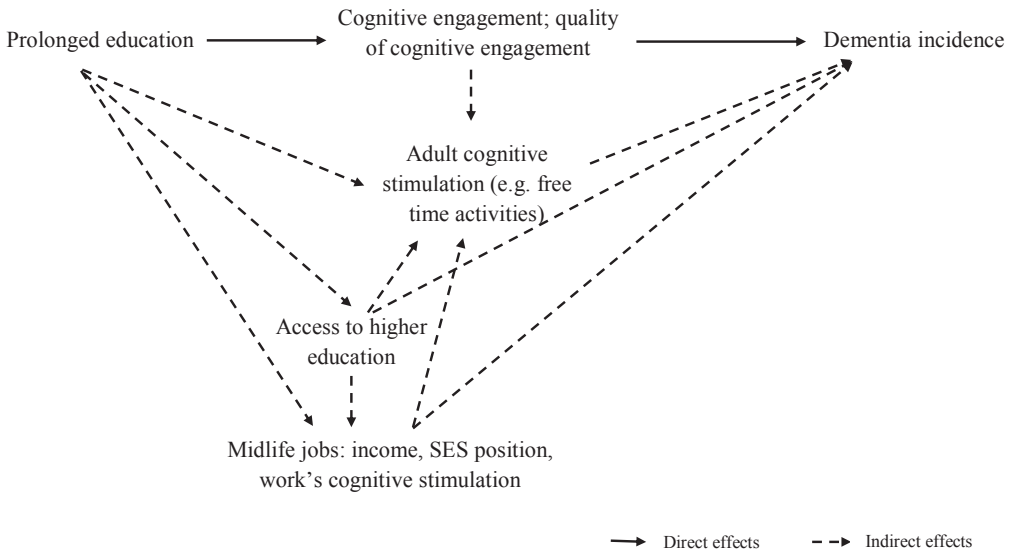


Figure 1. Schematics of some pathways linking prolonged education and dementia incidence. Note: The figure does not show exhaustive list of possibilities. We do not include childhood intelligence as the figure aims to illustrate pathways for an effect of an educational reform, which should not be biased by childhood intelligence.

1.5 KNOWLEDGE GAPS IN CURRENT RESEARCH

All in all, there is a large interest in understanding the relationships between education, cognitive aging, and dementia. This is partly due to the rising burden of dementia. However, many gaps in our knowledge remain.

First, there is a lack of updated evidence regarding dementia incidence in Sweden. Worldwide, circa 47 million individuals live with dementia at the moment, and by 2050 this number is expected to reach 135 million (Prince et al 2015). Such projections are based on studies examining dementia incidence and prevalence trends over time. There is a substantial number of studies examining dementia trends around the world (Wu et al 2017). Yet, thus far only one study considered incidence rates of dementia in Sweden by drawing on the relationship between prevalence and survival (Qiu et al 2013). The follow-up of that study ended in 2008. Therefore, updated studies that may corroborate earlier findings are needed.

Second, a debate remains regarding the potential causal effect of education on cognitive performance in early life. As highlighted above education is thought

to increase cognitive abilities. Several studies suggested that this relationship is causal when examining education and intelligence (Brinch & Galloway 2012; Carlsson et al 2012; Ceci 1991; Cliffordson & Gustafsson 2001). Yet, others view intelligence as fixed and highly heritable (Davies, Tenesa & Payton 2011; Deary, Penke & Johnson 2010). Furthermore, according to Cliffordson and Gustafsson (2008) effects of education on intelligence varied depending on focus of the curriculum. Nevertheless, heterogeneities of the possible causal effect with regards to social background have not been extensively examined.

Third, the association between education and level of cognition is robust (Opdebeeck, Martin & Clare 2016; Stenze 2007), a consensus regarding the association between education and decline in cognitive abilities has not been reached. Many individual studies exist, as well as summaries of the evidence. Nevertheless, they arrived at contrasting conclusions. Valenzuela and Sachdev (2006) found slower decline for individuals with higher education in their meta-analysis of 13 studies. Anstey and Christensen (2000) arrived at the same conclusion in their narrative review. Yet, the newest narrative review did not find reliable evidence for that conclusion (Lenehan et al 2014). In recent years, advanced statistical tools for analyzing change in cognition (e.g., linear or structural equation latent growth curve models) became widespread. Differences in methods or restrictions on study inclusion may be the reason for the diverse findings. Subsequently, comprehensive, systematic and conclusive review of the evidence is still missing.

Finally, there seems to be a causal effect of education on level of old-age cognition (Hamad et al, 2018), but less is known about the causal effects on dementia. A causal effect of education on dementia has been studied mainly using Mendelian randomization, which uses genetic variants as an instrument for assigning individuals to an exposure (Østergaard et al 2015; Nguyen et al 2016; Larsson et al 2017). The results of these studies reported mixed findings and showed low precision estimates. Furthermore, the genetic variants used are likely to affect both educational attainment and early-life cognitive ability, which would confound the estimate and violate the assumptions of the methods. One study used a quasi-experimental design exploiting variation education due to introduction of compulsory schooling reforms (Nguyen et al 2016). In that study, one-year increase in educational attainment predicted lower dementia probability by -9.5% (95% CI: –14.8, –4.2; $p < 0.001$) (Nguyen et al 2016). However, multiple reforms with diverse characteristics were studied, which limits discussion of potential mechanisms and timing of the exposure.

2 AIMS

2.1 OVERALL AIM

This thesis addressed the following question: What is the relationship between formal education and cognition (i.e. cognition in early adulthood, cognitive decline and neuropathological disturbances to cognition in the form of dementia) during the life-course? Further, the thesis discussed issues regarding the generation of evidence on causal relationships and inference of causation in epidemiology.

2.2 STUDY SPECIFIC AIMS

The overall aim was examined in four individual studies, which asked the following questions:

1) What is the burden of dementia among individuals with different levels of education over time in Sweden? *Study I*, titled "Thirty-year trends in dementia: a nationwide population study of Swedish inpatient records" addressed this question.

2) Is there a causal effect of education on intelligence in late adolescence and if so, is the effect equal for individuals from different socioeconomic backgrounds? *Study II* titled "Cognitive and emotional outcomes after prolonged education: a quasi-experiment on 320,182 Swedish boys" focused on these questions.

3) Is there a direct causal effect of education on the risk of old-age dementia? *Study III*, titled "Is there a direct causal effect of education on dementia: A Swedish natural experiement on 1.3 million individuals" considered this question.

4) Does the accumulated evidence from observational longitudinal studies indicate an association between education and decline in episodic memory? *Study IV*, titled "Education and age-related decline in episodic memory performance: Systematic review and meta-analysis of longitudinal studies" examined this question.

3 METHODOLOGICAL CONSIDERATIONS

A diversity of methods and designs was employed in this thesis. The studies ranged from an observational longitudinal study, through natural and quasi-experiments, to a summary of current evidence in the form of systematic review and meta-analysis of observational longitudinal studies. Employing a diversity of designs is important as it contributes to the triangulation of evidence.

3.1 DEMENTIA IN SWEDISH REGISTERS

Healthcare registers are useful resources for epidemiological research. For the purposes of this thesis, we examined the occurrence of dementia in several Swedish registers – namely the National Outpatient Register (Ludvigsson et al 2011), the National Inpatient Register (NIPR), the Cause of Death Register (CDR) and the Prescribed Drug Register (Wettermark et al. 2007). Dementia cases were ascertained in the National Patient Registers and in the Cause of Death Register, based on International Classification of Disease (ICD) codes. To ascertain if individual had dementia, all primary and secondary diagnoses or causes of death were considered. In the Prescribed Drug Register, Anatomical Therapeutic and Chemical (ATC) codes were used for identification of dementia cases (Table 2).

First, we examined an overlap between identified cases in the four data sources. For this purpose, the birth cohorts of 1920-1940 were followed. The CDR has national coverage since 1961, with historical register available also between 1952 and 1960 (Brooke et al 2007). The NIPR has national coverage since 1987, and almost complete coverage for psychiatric care since 1983 (Ludvigsson et al 2011). The Prescribed Drug register, which contains data on all dispensed prescriptions in Sweden, was established in July 2005 (Wettermark et al. 2007). While the National Outpatient Register was introduced already in 2001, the data quality varies substantially. According to senior statistician, who works with Swedish register data for epidemiological research, psychiatric diagnoses have reliable quality from 2006 and onwards (S Wicks 2018 personal communication). The National Outpatient Register includes outpatient physician visits to private and public institutions, and encompasses surgery and psychiatric care (National Board of Health and Welfare 2018). However, primary care visits are not included. Our study population was followed from 2006 through 2016. This period was selected to allow for equal length of follow-up in all registers.

Table 2. Codes used to identify dementia in Swedish Register data

Coding system	Years	Code	Description
ICD 10	1997 - onwards	F00.0	Dementia in Alzheimer's disease with early onset
		F00.1	Dementia in Alzheimer's disease with late onset
		F00.2	Dementia in Alzheimer's disease, atypical or mixed type
		F00.9	Dementia in Alzheimer's disease, unspecified
		F01.0	Vascular dementia of acute onset
		F01.1	Multi-infarct dementia
		F01.2	Subcortical vascular dementia
		F01.3	Mixed cortical and subcortical vascular dementia
		F01.8	Other vascular dementia
		F01.9	Vascular dementia, unspecified
		F02.0	Dementia in Pick's disease (Frontotemporal dementia)
		F02.3	Dementia in Parkinson's disease
		F03	Unspecified dementia
		G30.1	Alzheimer's disease with late onset
		G30.8	Other specified Alzheimer's disease
		G30.9	Alzheimer's disease, unspecified
		G31.1	Senile degeneration of brain, not elsewhere classified
		G31.8	Lewy-body dementia
ICD 9	1987-1996	290A	Senile dementia
		290B	Pre-senile dementia (onset before 65 years of age)
		290E	Multi-infarct dementia
		290W	Other specific dementia
		290X	Dementia not otherwise specified
		331A	Pre-senile or senile dementia of the Alzheimer type
ICD 8	1969-1986	290.00	Senile dementia
		290.10	Pre-senile dementia, Alzheimer's disease
		290.11	Pick's disease
		290.19	Pre-senile dementia, Creutzfeltdt-Jakob disease with dementia
		293.00	Cerebral arteriosclerosis
ATC	2005 - onwards	N06DA02	Donepezil drug prescription
		N06DA03	Rivastigmine drug prescription
		N06DA04	Galantamine drug prescription
		N06DX01	Memantine drug prescription

*ICD = International Classification of Disease; ACT=Anatomical Therapeutic and Chemical codes

Each register has identified a substantial number of unique cases (Figure 2). The majority (47.2%) of dementia cases was ascertained only in one register. Nearly one third (28.1%) of cases was identified in two registers, and nearly 16% in three registers. A small proportion (4.4%) of cases was identified in all four registers. Several previous studies have examined the sensitivity and specificity of dementia diagnoses in Swedish registers (Jin et al 2004; Nilsson et al 2016; Rizzuto et al 2018). Jin et al (2004) showed improved sensitivity if the two most commonly used registers (CDR & NIPR) were combined. They reported a detection rate for dementia diagnosis of 63% and nearly perfect specificity. The most recent validation study using five different population-based cohort studies also reported nearly perfect specificity (99,8% for NIPR and 99.0% for CDR) in the two registers (Rizzuto et al 2018). However, the study found relatively low sensitivity figures of 47.3% (95% CI: 44.1-50.5) for NIPR and 44.1% (95% CI: 40.9-47.4%) for the CDR (Rizzuto et al, 2018).

Using all available data sources may seem like a sound approach given the low-to-moderate sensitivity of the two most commonly used and examined registers. Low-to-moderate sensitivity results in a substantial number of missing cases. Given the large proportion of cases identified only in a single register, using more registers may to some extent mitigate this problem. However, such approach rests on the untested consistency assumption – in other words that for example having dementia diagnosis on the death certificate is equivalent to receiving dementia drugs. High specificity would suggest that, at least in the National Inpatient and Cause of Death Register, we do indeed identify dementia as we currently define by the "gold standard" in population-based studies. Yet, specificity and sensitivity are unknown for the National Outpatient Register and the Prescribed Drug Register.

Theoretically, if our coding described in Table 2 identifies "true" dementia cases (i.e. capture the same underlying disease processes), we should be able to estimate equivalent relationship between an exposure and dementia in the individual registers. To this aim, we have examined the association of education with old-age dementia separately in the four registers, using an equivalent follow-up (2006-2016) for the 1920-1940 cohorts. Cox proportional hazards survival models were used to estimate the association between education and the risk of dementia. The models had chronological age as the underlying timescale, and individuals entered the study on their 65th birthday. We included dummy variables identifying each cohort, to account for potential cohort trends, for example trends in healthcare seeking. Education was derived from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) (Statistics Sweden 2009), 1990 or 1970 census. Three categories (compulsory education, above compulsory education and at least some university) were created as described in section 4.1.2.

The association between education and the risk of dementia differed based on the register used (Table 3). Analyses based on National Inpatient Register and Cause of Death Register indicated an inverse association between education

and dementia diagnosis. On the other hand, those with higher level of education had a slightly increased hazard rate of receiving dementia drugs. Finally, those with higher education had higher risk of receiving dementia diagnosis in the National Outpatient Register. The registers identified different number of cases and varied with regards to average age of onset. For example, using the National Inpatient Register 7.8% of the study population was diagnosed with dementia at an average age of 83.5 (SD 5.3). On the other hand, according to the National Outpatient register only 5.1% of the population was diagnosed with dementia, with an average age of 80.9 years (SD 5.6). The equivalent figures for Cause of Death register were 8.1% and 85.3 years (SD 5.1) and for the Prescribed Drug register they were 7.6% and 80.7 (SD 5.3).

Thus, it seems plausible that the registers differ in their likelihood of capturing various types of dementia or different severity of the disease. For example, we would hypothesize that cases identified in the National Outpatient Register would

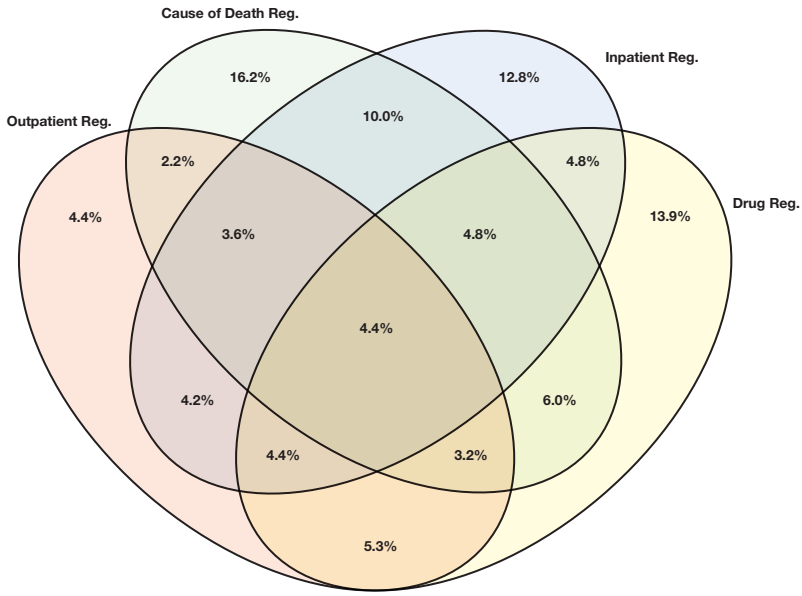


Figure 2. Overlap in old-age (65+ years of age) dementia cases identification between four Swedish registers (the National Inpatient Register, the National Outpatient Register, the Cause of Death Register and the Prescribed Drug Register). The overlap is based on 1920-1940 cohorts, followed up for equal time in all registers between 2006 and 2016. All diagnoses (primary or secondary) and all causes of death (main and underlying) were considered. In the Prescribed Drug Register, Anatomical Therapeutic and Chemical codes were used for identification of dementia cases. Percentage in each intersection of ellipses corresponds to the proportion of total identified cases in that category. Note: the size of the ellipses is not proportional to size of the group.

be less severe than those identified in the National Inpatient Register. Subsequently, confounders, which may bias the relationship between exposure of interest and dementia, may differ across the data sources. There can also be different confounders of systematic misclassification of the cases in each data source. One important confounder is level of comorbidity. Therefore, in further analyses we also adjusted the models for weighted Charlson Comorbidity Index, which strongly predicts mortality among the older population (Quan et al 2005). However, the results (not shown) remained unaltered. Overall, the consistency of dementia diagnoses, for example with regards to severity, across the registers remains to be examined. Further, confounders of misclassification in individual registers also warrant further attention.

Due to the lack of knowledge of possible register specific confounders, we used only the National Inpatient Register (*Study I* and *III*) and the Cause of Death Register (*Study III*) to ascertain dementia for the studied individuals. Codes, based on a study by Jin et al (2004) and specified in Table 2, were used in both registers. A multiple-cause approach, which considered all primary and secondary diagnoses and main and contributing causes of death was employed. Such an approach has been suggested for chronic diseases, where physicians may be less precise in specifying main and secondary causes (Garcia-Ptacek et al 2016). Furthermore, given the low sensitivity but high specificity, such an approach is preferable.

Overall, all hospital admissions regardless of their length were considered. Given the neurodegenerative nature of dementia, with progressive worsening, we used the date of the individual's first hospitalization with dementia to assess the timing of diagnosis. If the cases were ascertained through the Cause of Death Register, the date of death was used as the timing of dementia. All hospital admissions, regardless of length of stay, were considered.

Table 3. Results of four Cox proportional hazards survival models examining the association between education and dementia in four Swedish national registers. All models used chronological age as the underlying time-scale, are sex adjusted and individuals enter study at 65 years of age.

	National Inpatient Register	Cause of Death Register	Prescribed Drug Register	National Outpatient register
Education	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Compulsory	ref.	ref.	ref.	ref.
Above compulsory	0.95 (0.93-0.96)	0.91 (0.89-0.92)	1.04 (1.02-1.05)	1.17 (1.15-1.19)
At least some university	0.81 (0.79-0.83)	0.78 (0.76-0.79)	1.03 (1.01-1.05)	1.27 (1.24-1.30)

HR = Hazard rate, CI = Confidence interval

3.2 EDUCATION IN SWEDEN

3.2.1 Educational system in Sweden in the 20th century

The birth cohorts studied in this thesis were in school from the late 1920s to the mid-1960s. During this time, the Swedish school system changed substantially (Figure 3). At that time, Swedish children entered first grade the year they turn seven. In the 1930s and the 1940s, children started in a primary school called Folkskola, which was free of charge. However, already after three years some children could leave this school form since multiple pathways through the educational system were available due to academic tracking (Figure 3-a&b) (Fischer et al 2018).

The length of the primary schooling changed over time. Prior to 1936, compulsory attendance of six years was the norm, even though there were some exceptions. In order to match the longer educational standard in Western Europe and the US, the Swedish parliament passed a bill stipulating a primary schooling extension in 1936. The law required adoption of a seventh year of primary schooling (Folkskola) by all school districts prior to 1949, and resulted in what we henceforth call the primary schooling reform (Fischer et al 2018).

The primary schooling reform was relatively straightforward - it added one more year of education for children at the age 13, who were attending the type of primary schooling ("Folkskola") affected by the reform (Figure 3-b). Prolonging education was deemed necessary in order to cover the contemporary curriculum. About 70% of the children at the time completed their education in this school type. The remaining pupils had left this track for more academically focused junior secondary school ("Realskola") (Figure 3-a&b). In order to attend the more academic track, pupils had to complete an entrance exam. Subsequently, pupils were segregated according to skills, but also socioeconomic background. Nevertheless, at the time, the majority of pupils attended the type of schooling affected by the reform. As a consequence, a large proportion of the population experienced an increase in educational attainment. On average, the education was prolonged by 0.7 years (Fischer et al 2018).

A later reform initiated in 1949, henceforth called the comprehensive school reform ("Enhetskolereformen"), changed the entire schooling system (Figure 3-c). In order to increase equality of opportunity, tracking prior to upper secondary education ("Gymnasium") was abolished. Therefore, all pupils stayed together during the primary schooling (Holmlund 2008). The reform was implemented gradually, and it also extended the compulsory education from eight to nine years. Subsequently, the reform made lower secondary education compulsory. Furthermore, some curriculum changes occurred. For example, English became a compulsory subject already in 4rd and 5th grade (Holmlund 2008).

The two reforms differed substantially in their content, implementation, and also had diverse effects on further educational attainment. While the primary schooling reform prolonged education, it only had a small effect (~1%) on further

educational attainment (Fischer et al 2018). In contrast, the comprehensive school reform made more pupils qualified for post-compulsory schooling by abolishing tracking, and more pupils did indeed continue to higher education.

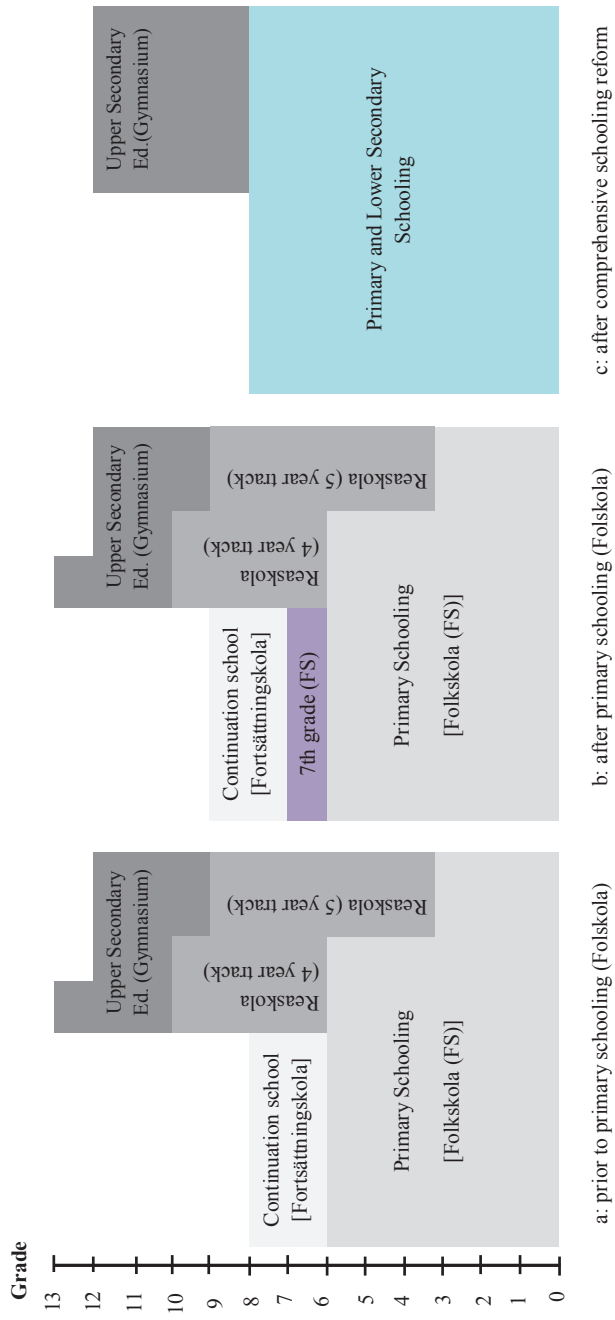


Figure 3. Schematic illustration (simplified) of the Swedish lower educational school system during different time periods of the 20th century: (a) prior to 1936; b) between 1936 and 1949; c) between 1949 and 1969. The figure was based on and adapted from Fischer et al 2018. Continuation school was a low intensity education of six weeks per year. Note: In Study II, we use the term elementary school for Folkskola, instead of primary school and junior secondary school for Realskola type education. University education is not displayed.

3.2.2 Education variables assignment

This thesis exploited variation in education caused by the comprehensive school reform (*Study II*) and the primary schooling reform (*Study III*). In addition, two other educational measures were used. First, years of education are used in *Study II, III* and *IV*. Second, the highest achieved degree, grouped into three larger categories, was used in *Study I* and *Study III.* In *Study IV* we relied on measures from the original articles (continuous, binary or ordinal) and rescaled them to years of education. Overall, this section provides a background on the educational variables used, their operationalization and assignment for individuals in our study populations.

The primary schooling reform was implemented at the school district level. At the time, the school districts typically coincided with church parishes (Fischer et al 2018). Furthermore, the mother's church parish was usually the unit for registration of new births. Thus, we used this correspondence to assign individual's exposure to the primary schooling reform. First, data on year of reform implementation at the school district level was manually collected from historical catalogues from 280 Swedish regional archives (Fischer et al 2018). Second, we obtained the parish of birth from the Multigenerational register (Statistics Sweden 2017) provided to us by Statistics Sweden. Finally, we merged the reform exposure to the individuals in the study population, assuming an agreement between the parish of birth and the school district.

The comprehensive school reform was implemented at the municipal level. Every year, a number of municipalities was selected to adopt the reform by the government. At the same time, a number of similar municipalities was kept as controls. For this selection procedure, the municipalities had to report their characteristics, such as population growth, tax revenues and demand for education (Holmlund 2008). Gradual implementation was selected in order to evaluate the effectiveness of the changes on children's achievements. Since the reform implementation occurred at the municipal level, we used the municipality of residence at the schooling age (7-11 years) from the 1960 census (for the 1951-53 cohorts) and the 1965 census (for the 1954-58 cohorts).

We also used educational data from Swedish registers. We obtained data from LISA (Statistics Sweden 2009), which in turn derives information from the Educational register (Statistics Sweden 2018). In LISA, the data is entered as SUN2000 classification codes, with three position specification. The SUN classification is comparable to the International Standard Classification of Education (ISCED97). We converted the 39 categories to 7 levels according to Statistics Sweden's documentation (Statistics Sweden 2009) (Table 4).

Further, we used the 1990 census data, which had a two-position specification for the educational variable. The variable specified the level and at times also the specialization of schooling. We have converted the data to the same 7 levels used for the variable from LISA (Table 4). Finally, we used educational information

from the 1970 census. This variable has only seven levels, but they differ from the two previous variables (Table 5). In *Study I* and *III*, we used three larger analytical categories: 1) compulsory schooling/elementary schooling only; 2) above compulsory schooling; and 3) at least some university (Tables 4 & 5). In some analyses, those with missing data were included as a separate category.

The final measure we used (*Study II* and *Study III*) were years of education. In Study II, years of education were derived from the Educational register, using the typical length of schooling associated with the individual's highest achieved academic degree. The variable was truncated to the number of years that could take place before conscription. In Study III, we constructed a measure for years of education based on the 1970 census. Two variables – highest completed schooling degree and highest completed post-schooling degree (e.g. vocational training or university) – were used. Each level of the two variables was assigned a typical number of years needed for its completion. The final constructed measure added the number of years for each variable (i.e. years of schooling + years of post-schooling). Subsequently, this constructed measure has higher variation in length of schooling, as it also accounts for variation in lower schooling (Fischer et al 2018). The typical measure considers only length of education associated with the highest achieved academic degree. We used the typical measure in sensitivity analyses.

3.3 MATERIALS IN STUDY I

Study Sample

A study cohort was created by linking multiple Swedish registers with the help of a unique individual identifier, corresponding to the personal number (equivalent to social security number) (Ludvigsson et al 2009). The follow-up period spanned 30 years, from 1987 through 2016. We used the Total Population Register (Ludvigsson et al 2016) to define the study population for every calendar year during the study period. Individuals were included either from the year they turned 65 years, or from the first year above that age that they were registered as residents in Sweden (Seblova et al, 2018). We excluded individuals (0.64%) with repeated migrations (>1 migration) after 65 years of age, because it was unclear if they obtained healthcare in Sweden and our outcome was defined using the Swedish National Inpatient Register (NIPR). Further, we excluded those that received dementia diagnosis in their inpatient records prior to age 65 (0.19%). The per calendar year sample size ranged from 972,167 in 1987 to 1,991,483 in 2016.

Education exposure

In order to assess the dementia for individuals with different level of formal education, we used information on education from LISA, or, if the variable was missing in LISA, from the 1990 or 1970 census. The larger analytical categories (elementary school, high school and at least some university education) were used (Tables 4 & 5).

Those with missing data on education were included as a separate category in the analyses, and corresponded to 2.9% of the overall sample (range per year, 2.5%–3.7%).

Table 4. Description of conversion of educational variables from LISA and 1990 census to larger categories.

Category	LISA 1990 code starts with:	1990 census code equal to:	Analytical category:
Primary schooling < 9 years	1	01;	Compulsory Schooling/ elementary schooling
Primary schooling = 9 years	2	02;	
High school max. 2 years	31 & 32	03; 06; 10; 30; 40; 45; 46; 47; 59; 65; 66; 72	Above compulsory schooling / at least some high school
High school = 3 years	33	04; 05; 22;31; 32; 33; 48;	
University < 3 years	41 & 52	07; 11; 12; 13; 14; 15; 16; 23; 34; 35; 41; 49; 50; 51; 52; 53; 60; 61; 67; 68; 73	At least some university
University => 3 years	53; 54; 55	08; 17; 18; 19; 20; 21; 24; 25; 26; 27; 28; 36; 37; 38; 42; 53; 44; 54; 55; 56; 57; 62; 63; 69; 70; 74	
PhD	6	09; 29; 39; 58; 64; 71; 75	
Missing	9 or missing	00, 76 or missing	Missing

Table 5. Description of conversion of educational variables from 1970 census to larger categories.

Category	Analytical category:
Primary schooling (Folkskola) <= 7 years Primary schooling (Folkskola) = 8 years; incomplete Realskola Primary schooling = 9 years (several types)	Compulsory Schooling/ elementary schooling
Realskola, incomplete high school (Gymnasium) High school (Gymnasium)	Above compulsory schooling/ at least some high school
Post-high school education University => 3 years	At least some university
Missing	Missing

Outcome: Incidence of dementia diagnosis

The NIPR records were used to calculate the incidence of dementia diagnoses in Swedish hospitals per every calendar year of the follow-up. The year of first hospital diagnosis of dementia during the follow-up period for a given person was considered as incidence timing. The follow-up period spans two ICD systems: ICD 9 and ICD 10. Therefore, appropriate codes were used (Table 2) and our approach to ascertaining dementia cases is detailed in section 4.1.1.

Covariates

Not all ages were observed during all follow-up times. Therefore, we used five-year age group strata. Since age strongly influences dementia incidence, our statistical models adjusted for age continuously (in years) within every five-year age category. Previous studies reported heterogeneous associations by sex. Therefore, the descriptive analyses were stratified by sex and the multivariate analyses included sex as a covariate.

Due to our use of healthcare data, we also included several time-varying healthcare practice confounders. First, a dummy indicating the ICD period was included, since change in diagnostic criteria may alter diagnostic practice and previous research suggested that the two systems have various levels of sensitivity (Quan et al 2008). Second, during the follow-up, a reformation of care for older adults was implemented via the Elderly Reform Act ("Ädelreformen"). The reform shifted the responsibility for social and some medical care from county councils to municipalities. Subsequently, the reform may have affected the rate of hospitalizations. Therefore, the statistical models included a dummy indicating the pre- and post-reform periods. Third, hospitalization frequency may vary over time and by sex, age and educational level. Hence, we calculated a proportion of all-cause hospitalizations per calendar year and per age-, sex- and educational strata. The multivariate models included the proportion as a time-varying variable in order to control for the possibility that our observed trends are driven by trends in all-cause hospitalizations.

3.4 ANALYSIS IN STUDY I

As a descriptive analysis, we computed, and graphically visualized the per calendar year incidence rates of dementia per 10,000 individuals aged 65 years or older in five-year age strata, and in three educational strata. The aforementioned rates were calculated separately for women and men.

In the multivariate analyses, we employed discrete time logistic models with a complementary log-log link (cloglog) function. We used individual level data with one observation per calendar year in which the person was included in the study. Subsequently, we obtained hazard ratios that capture the risk of receiving a hospital diagnosis of dementia for a person that survived to 65 years of age and is in a specific age- and education- strata. We first estimated crude models for one calendar year increase for every age group strata, in order to assess the changes in incidence

of dementia in hospital records over time. To examine the educational gradient in dementia incidence we added education to the models, while controlling for age (continuous), sex, and the healthcare practice confounders (see above). In order to study the stability of the dementia incidence by educational levels over time, we added an interaction term between education and calendar year, if there were significant main associations.

3.5 MATERIALS IN STUDY II

Study sample

Eight birth cohorts (1951-1958) of Swedish men were included if they were part of the 1960 or 1965 census. The conditioning on availability of census data was necessary in order to assign comprehensive school reform exposure. While more cohorts were affected by the studied reform, the sample was restricted to these cohorts in order to keep the outcome assessment consistent. The eligible sample was 427,181 men from 1,030 municipalities with per cohort range in sample size from 51,980 to 54,597. After excluding those without reform exposure, conscription records, and without known childhood socioeconomic position (SEP) 320,182 men remained (Figure 4).

Exposure – the comprehensive school reform ("Enhetskolereformen")

This study used the comprehensive school reform, which was explicitly designed as a quasi-experiment by the government. Along with other changes, the reform prolonged compulsory education from eight to nine years. It was implemented gradually over time and regions (i.e. more than 1000 municipalities). Thus, some municipalities adopted changes stipulated by the reform, while similar municipalities followed the old system and were kept as controls. In summary, the reform resulted in spatial and temporal variation in education that we leverage to study the causal effect of education on intelligence. We determined reform's status by ascertaining municipality of residence at schooling ages (7-11 years). For boys born 1951-1953 we used the 1965 census and for those born 1954-1958 we used the 1965 census.

Outcome – intelligence

Intelligence was derived from conscription data, which were available for 98.1 % of boys for whom it was possible to determine experimental status. Swedish men were tested at conscription, and if eligible they started their service later. The conscription tests measured various cognitive abilities. The first test, called "Instructions", tested verbal ability by asking the respondent to follow 40 commands (e.g. strike the fourth number, put a ring around a second one). The second test of "Concept discrimination" included 40 items targeting verbal and reasoning abilities. The men had to choose a concept that did not belong in a list of five. The third test, a variation of the Minnesota Paper Form Board, had 25 items measuring visuospatial abilities. The men had to choose one out of four sets, which would form a certain figure. The fourth and final test examined "Technical comprehension" with 52 questions with figures and questions regarding a technical problem.

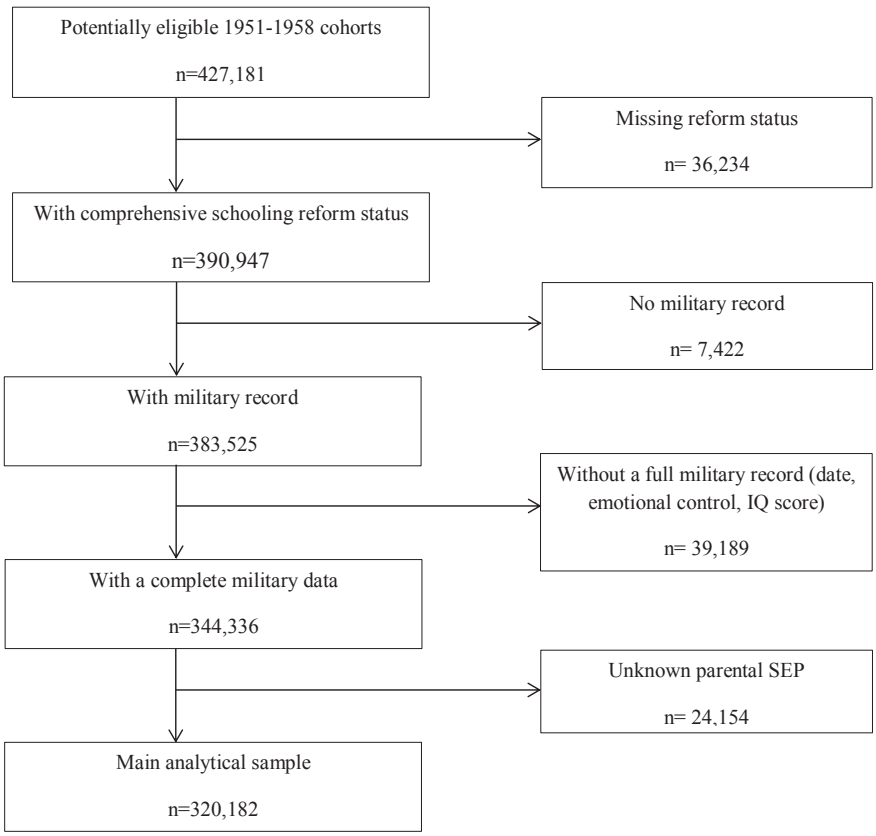


Figure 4. Study II sample derivation flowchart with details regarding the reasons for exclusion.

A single latent score of general intelligence was derived based on scores from the individual tests with structural equation modeling. The models were based on 413,511 men for whom we had test scores, even if other variables were missing. The four tests had adequate loadings on the latent score (Instructions: 0.87; Concept discrimination: 0.84; Paper Form Board: 0.61; and Technical comprehension: 0.66). In our analyses we used standardized intelligence latent scores (mean 100, SD 15).

Childhood socioeconomic position

To assess if the possible reform effect on intelligence differed for men from different social backgrounds, we derived childhood SEP using either the 1960 or 1965 census. Parents were linked to their offspring using the Multigenerational register (Statistics Sweden 2017). Parental occupation was grouped according to the Swedish Socioeconomic Classification scheme. When parents had different SEP, the higher one was used. Sons of professionals were a small group (n=1,273), and thus were collapsed with the high non-manual workers group.

3.6 ANALYSIS IN STUDY II

We used multilevel linear regression with fixed municipality effects to evaluate the impact of the reform on intelligence. Standard errors were clustered at the municipal level. First, we estimated models for all men for whom we had information on childhood SEP. We extended this model and added an interaction between the reform indicator and childhood SEP (entered as a continuous variable) in order to evaluate presence of differential effect by SEP. Second, models stratified by childhood SEP were estimated and included those with missing childhood SEP as one stratum.

All the aforementioned models were adjusted for month of birth categorically. Hence, each month starting with January 1951 and ending with December 1958 was assigned a dummy. We adopted this approach to flexibly control for confounding by seasonality of birth effects and/or cohort differences. We also control for age at testing (in months) in a similar manner. As a sensitivity analysis, we limited our sample and applied a pre-post design. Thus, we kept only those observations from municipalities for which we had data both before and after the reform introduction (n=142,221).

3.7 MATERIALS IN STUDY III

Study sample

The study sample included 18 Swedish birth cohorts (1920-1937), which were identified using the Total Population Register. While those born prior to 1920 could have been affected by the studied reform, we did not observe the expected increase in dementia with increasing age. Therefore, we limited the study to cohorts, where the outcome data quality was deemed sufficient. Similarly, younger cohorts could have been affected. Nevertheless, younger individuals could have also been subject to the comprehensive school reform,

which could confound the studied effect. Overall, our study cohorts included 1,972,038 men and women. After excluding those who died, emigrated, received dementia diagnosis prior to their 65th birthday or for whom we could not determine exposure status, 1,341,842 individuals remained (Figure 5).

Primary Exposure – the Primary Schooling Reform ("Folkskolarefomen")

This study used the primary schooling ("Folkskola") reform that prolonged education from six to seven years. The reform was initiated by 1936 governmental bill, and the extra year had to be adopted by school districts prior to 1949. The implementation was not random, since the districts could choose when to implement the reform. Yet it generated spatial and temporal variation due to gradual adoption across the 2,463 school districts (Figure 6). We leveraged this variation as a natural experiment in order to study causal effect of education on dementia.

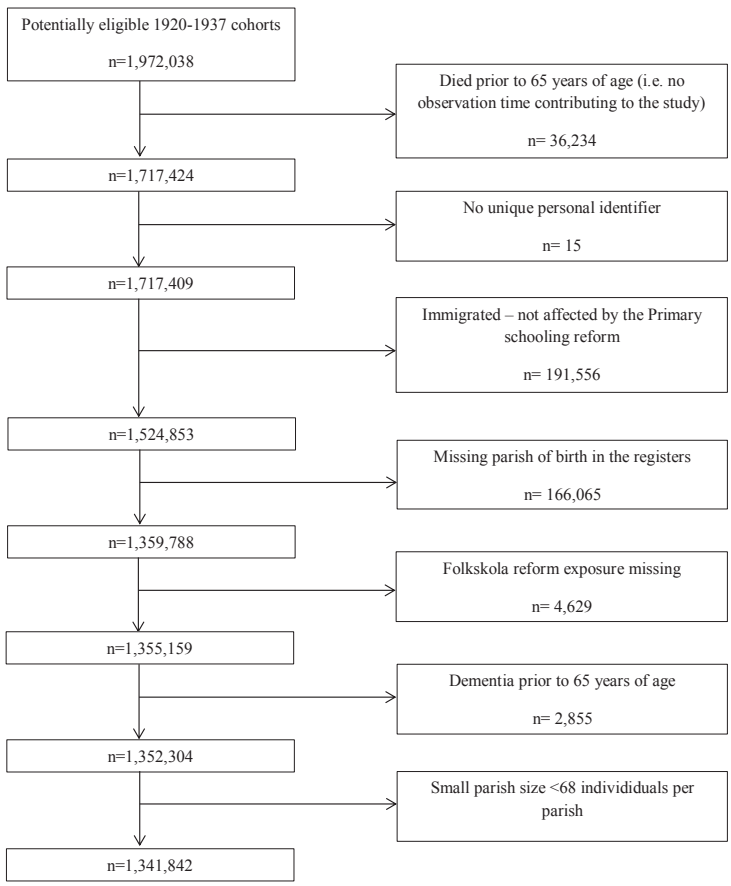
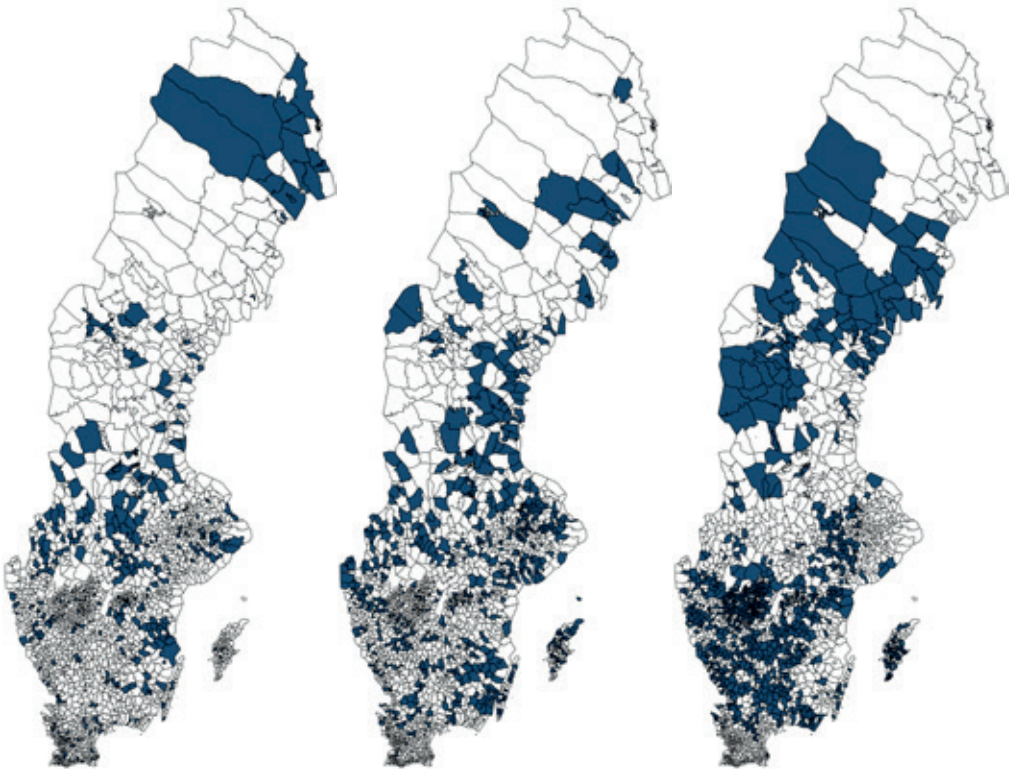


Figure 5. Study III sample derivation flowchart with details regarding the reasons for exclusion.

Outcome – Dementia in Swedish registers

We used the National Patient Register and the Cause of Death Register to ascertain if an individual obtained dementia diagnosis. The follow-up period spanned from 1985 through 2016, and thus ICD 8, 9 and 10 codes were used (Table 2). We used the multiple-causes approach described above (see section 3.1.1). A previous study reported low-to-moderate sensitivity (app. 50%) for dementia diagnosis in the NIPR and CRD (Rizutto et al 2018). To better understand possible outcome misclassification in this specific study we obtained education stratified estimates



a) 1936-1941 b) 1942-1957 c) 1948-53

Figure 6. Timing of the introduction of the 7th year due to the primary schooling ("Folkskola") reform. The geographical units in the maps are church parishes, which generally correspond to the school districts. Note: The figure was created by Martin Fischer, published in (Fischer et al 2018). Reproduced with permission.

for our cohorts (1920-1937) based on the newest validation study (Rizzuto et al, 2018). When both registers were combined and follow-up started in 1985, the sensitivity for our cohorts was 73.9% (95% CI: 64.7-81.8%) for those with less than eight years of education and 68.2% (95% CI: 55.6-79.1%) for those with at least eight years or more. Thus, for our cohorts and follow-up the dementia sensitivity was higher than previously reported and there was no evidence of differential sensitivity by educational level although statistical power of these analyses was low.

3.8 ANALYSIS IN STUDY III

One overall and two sex-stratified Cox proportional hazards models, with stratified baseline hazards, were estimated to assess the causal effect of the primary schooling reform on the hazard rate of dementia. Chronological age was used as the underlying time scale and individuals entered the study on their 65th birthday. All models included a dummy variable for every cohort in order to capture possible cohort trends. Further, the model for the entire sample controlled for sex. Since the reform exposure was assigned at the school district/parish level, all Cox models had stratified baseline hazards at the school district/parish level. Robust standard errors were also clustered at the school district/parish level. Multiple sensitivity analyses, assessing misclassification, differences in healthcare-seeking behavior or employing pre-post design were also carried out (see details in *Study III*).

3.9 MATERIALS IN STUDY IV

In order to examine the accumulated evidence regarding the association between education and decline in episodic memory, we conducted a systematic review and meta-analysis. Thus, the materials for this study were already published peer-reviewed longitudinal studies that reported on relationship between education and change in episodic memory. The systematic search is described in detail in *Study IV*. Briefly, we searched four databases (PubMed, PsycInfo, Web of Science and Embase) with keywords related to three areas: 1) cognitive performance, 2) change over time, and 3) education. Identified non-duplicate records (n=6,379) were screened for inclusion first by title, then by abstracts and finally full text articles were reviewed (Figure 7). Articles reporting quantitative estimates with all required details, and which used unique cohort data, were included in the meta-analysis (n=15). The rest of eligible studies (n=24) were summarized qualitatively. The data needed for qualitative or quantitative summary were extracted from each article and for every independent longitudinal cohort reported within the article. Articles reporting on the same cohorts, using the same episodic memory measure, were further evaluated and those with larger sample and longer follow-up were included in the quantitative summary.

3.10 ANALYSIS IN STUDY IV

For the quantitative analysis, the estimates reported in the individual articles were converted to the same metric. Therefore, we rescaled them so they corresponded to an association of one additional year of education with change in episodic memory (in SD) per decade. Provided baseline SD or recalculated one (from 95% CI or SE) was used for the rescaling. For articles using

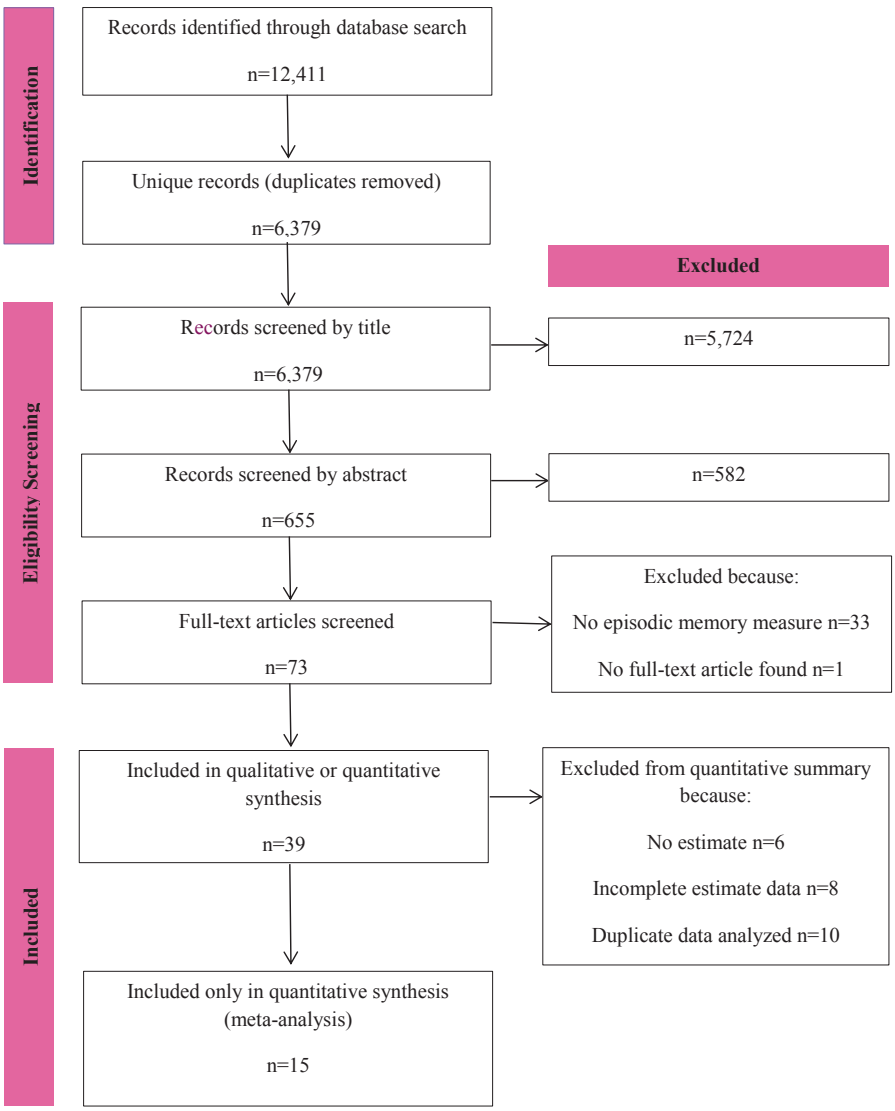


Figure 7. Flow chart of the systematic literature search and the screening process for the systematic review and meta-analysis of longitudinal studies examining the association between education and change in episodic memory.

binary or ordinal educational measures, we used the average difference between the most extreme educational categories for the rescaling. If an article provided multiple episodic memory measures from the same sample, we recalculated (i.e. pooled) the estimate and related variances.

To calculate the meta-analytic estimate, we executed an inverse-variance weighted random effects meta-analysis (Viechtbauer 2010). We chose random-effects approach because of its weaker assumption regarding homogeneity of the association across contexts. In order to assess if some study specific factors were associated with the meta-analytic estimate, we performed a meta-regression. The factors considered were: mean age, mean educational attainment, and maximum follow-up period. We assessed heterogeneity (Cochran's Q and I^2), publication bias and ran sensitivity analyses removing outliers.

3.11 OVERALL ETHICAL CONSIDERATIONS

Studies using primary data (*Study I, II & III*) were approved by the Stockholm's Regional Ethical Review Board (DNR 2010/1185-31/5 and DNR 205/556-31). The three studies were register-based and thus predominantly used personal data collected for administrative purposes. *Study IV*, analyzed data from previously published articles at an aggregate level and subsequently, did not require an ethical permit.

Protection of human subjects is a key ethical issue in medical research (World Medical Association 2001). Often, written informed consent is required, especially when sensitive data, such as medical information, is used. Nevertheless, the use of secondary data complicates obtaining informed consent. In the case of register-based studies, a pragmatic approach to consent is usually adopted. Therefore, project descriptions, information about the possibility to opt-out, and contact information for the responsible researchers should be publicly available. Nonetheless, some individuals may not be aware that administrative data, which includes their information, is used for research.

Subsequently taking steps to protect individual's integrity is of paramount importance. For this reason, all data are pseudonymised and the key connecting research identification number to the personal identification number is available only to the authorities in charge of the data. Furthermore, harm-benefits analysis of the proposed research is considered by the Ethical Review Board and legal aspects of data safety are further assessed by the authorities releasing data. All above steps were adopted in our studies. Finally, two of our studies (*Study II & III*) aim at estimating a causal effect and the thesis overall is concerned with causal inference in epidemiology. We believe that when discussing possible causal conclusions, even higher caution in presenting and interpreting the results is warranted. Yet careful interpretation of all findings, those regarding an associations or causal relationship, is needed and of ethical concern.

4 OVERWIEW OF RESULTS

4.1 STUDY I: INCIDENCE OF DEMENTIA IN INPATIENT RECORDS BY EDUCATION

Over the entire period the crude dementia incidence rate in the inpatient records displayed an educational gradient, presenting an inverse association between education and dementia (Figure 8). When stratifying by five-year age groups and educational level the dementia incidence rate showed educational gradient up to age 90 (Figure 8) during most of the follow-up years. Additionally, dementia incidence showed levelling off or decline in majority of educational and age strata in the last half a decade of the follow-up period. The above results were consistent when stratifying the analyses by sex.

The results from the discrete time logistic models within each age-strata also showed an educational gradient in the risk of receiving dementia diagnosis in hospital up to age 90 (Table 6). The models were adjusted for calendar year, age (continuous), sex and healthcare variables. The descriptive plots (Figure 9) did not show substantial differences in dementia incidence trend by educational level. However, when an interaction term (educational level by calendar year) was included in the age-stratified models, it indicated that the trend differed by educational level for all models where education had a main effect (i.e. under 90 years of age).

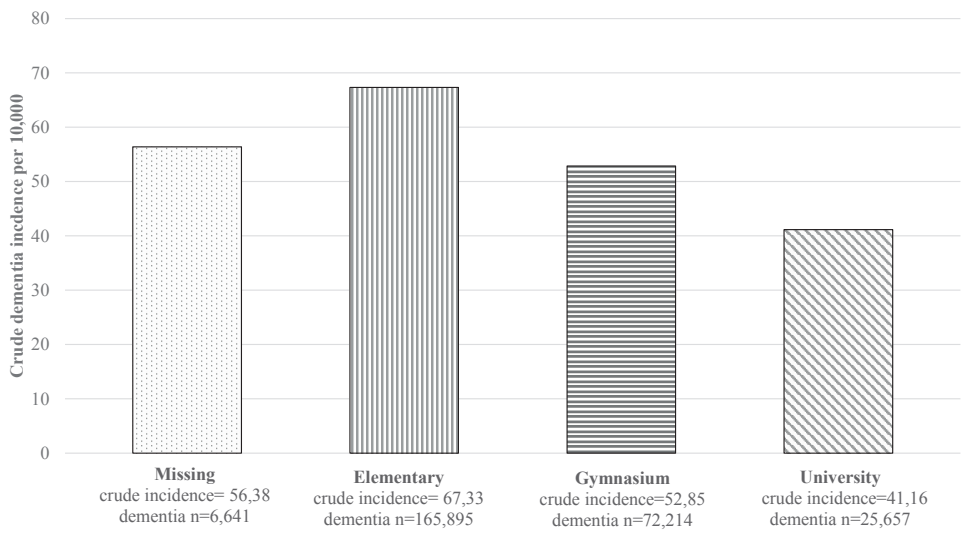


Figure 8. Crude dementia incidence in inpatient records by educational levels during entire follow-up (1987-2016).

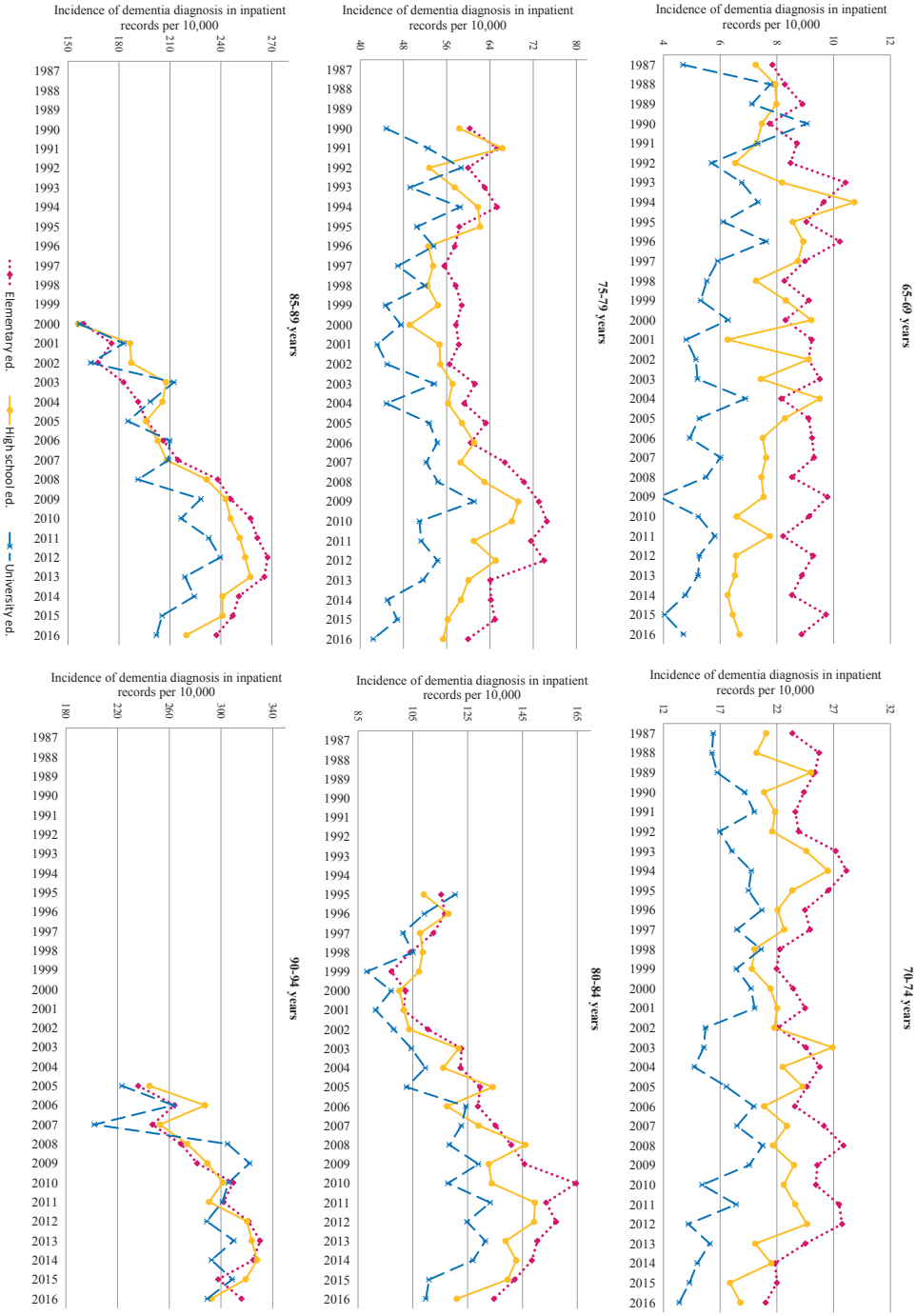


Figure 9. Age and education-stratified rates (per 10,000) of first diagnosis of dementia in hospital inpatient records for every year of follow-up. Note: the highest age strata (95+) was omitted in this figure, but is reported in Study I. Note: ed.= education

Tab 6. Results from cloglog regressions models reporting results for education, stratified by age strata. The models estimate a hazard ratio (HR) that a person surviving to given age strata would receive a hospital diagnosis of dementia.

Age strata	Missing ed.		Elementary		High School		Interaction**: calendar year*ed.
	HR*	95% CI	HR*	95% CI	HR*	95% CI	p-value
65-69	1,68	1.49-1.89	1,51	1.41-1.61	1,34	1.25-1.42	<0.001
70-74	1,36	1.25-1.47	1,35	1.29-1.40	1,25	1.20-1.31	<0.001
75-79	1,18	1.12-1.26	1,22	1.18-1.26	1,16	1.12-1.19	<0.01
80-84	1,12	1.06-1.19	1,13	1.10-1.16	1,10	1.07-1.13	<0.01
85-89	1,07	1.01-1.14	1,09	1.06-1.12	1,08	1.05-1.12	<0.001
90-94	0,99	0.90-1.09	1,03	0.98-1.07	1,03	0.99-1.08	N/A
95+	0,78	0.61-0.99	0,94	0.85-1.05	0,98	0.87-1.11	N/A

Those with university level were used as a reference category. If there were significant main effects, up to 3 interaction models were estimated for every age group strata.

*Adjusted for calendar year, age (continuous within each strata), sex, and healthcare variables.

** Interaction models did not adjust for healthcare variables.

4.2 STUDY II: EFFECT OF THE COMPREHENSIVE SCHOOL REFORM ON INTELLIGENCE

The comprehensive school reform had an impact on IQ at conscription. Among those with known childhood SEP, those exposed to the reform had 0.75 IQ units (95% CI 0.42 to 1.09; p<0.0005) higher latent cognitive score than those unexposed (Figure 10). In the pre-post sensitivity analyses, the effect remained and those exposed had 0.64 IQ units (95% CI: 0.34-0.94; p<0.0005) higher latent cognitive score than those unexposed. We examined effect heterogeneity by childhood SEP among those with socioeconomic data. The interaction term between the reform indicator and childhood SEP (added as continuous) had a p-value of 0.067.

However, the childhood SEP stratified models indicated that the effect differed for men from different backgrounds. The differences between exposed and unexposed were highest at the lowest end of the childhood SEP spectrum, i.e. for sons of farmers, unqualified manual workers and qualified manual workers (Figure 10). At the higher end of the childhood SEP spectrum (i.e. for sons of entrepreneurs, low-, middle-, and high non-manual workers and sons of professionals) there were no major differences between men exposed and unexposed to the educational reform.

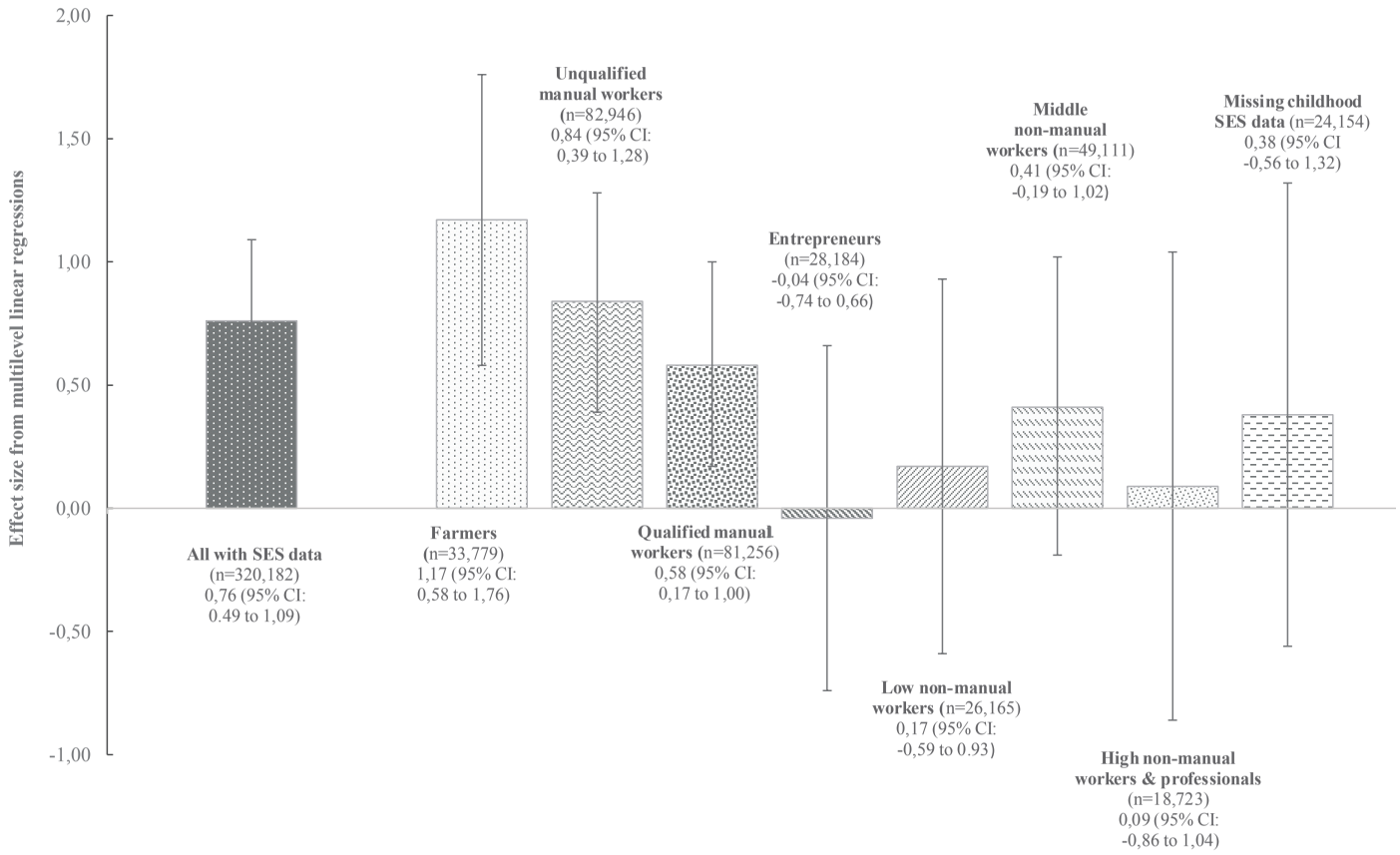


Figure 10. Effect of the Swedish comprehensive school reform ("Enhetskolereformen") on men's IQ latent cognitive score derived from four intelligence tests at conscription. IQ units are standardized (mean 100, SD 15). Point estimates and 95% CI are derived from multilevel linear regressions with fixed municipality effects and standard errors clustered at the municipal level.

4.3 STUDY III: EFFECT OF THE PRIMARY SCHOOLING REFORM ON DEMENTIA

In our study sample, there were 192,638 cases of dementia during the follow-up period. Thus, 14.3% of the sample received a dementia diagnosis, at an average age of 82.4 (SD 6.1). The majority (79%) received their dementia diagnosis from the National Inpatient Register. More than half of the cohort (55.2%) had their education prolonged from six to seven years due to the primary schooling reform. There were no statistically significant differences in risk of receiving dementia diagnosis in inpatient records or on death certificates for those exposed to the primary schooling reform (HR 1.01; 95% CI 0.98-1.04), compared to those unexposed. Sex-stratified analyses did not alter the conclusion (Table 7), nor did any of the sensitivity analyses (see *Study III* for details).

Tab 7. Descriptive data and results from Cox proportional hazards models with stratified baseline hazards at the school district level. The models examined the causal effect of prolonged education due to the primary schooling reform on hospitalization or death with dementia diagnosis. All models adjusted for cohort trends by including a dummy variable for every cohort and had robust standard errors clustered at the school district level.

Sample	n	n dementia (%)	n treated (%)	HR (95% CI)
All individuals*	1,341,842	192,638 (14.3)	740,989 (55.2)	1.01 (0.98-1.04)
Men	652,623	80,538 (12.3)	361,547 (55.4)	1.02 (0.99-1.06)
Women	889,213	112,100 (16.3)	379,442 (55.1)	1.01 (0.97-1.04)

*Sex-adjusted; HR= Hazard ratio; CI= Confidence interval

4.4 STUDY IV: EDUCATION AND DECLINE IN EPISODIC MEMORY

A majority (n=17; 70%) of the articles in the qualitative summary did not report any significant associations between higher education and change in episodic memory. Out of the remaining seven articles, four reported faster decline in more educated individuals and three found the opposite. Our pooled meta-analytical estimate, based on 35 point estimates from 15 articles, did not indicate any significant association between an additional year of education and the change in episodic memory (β=0.0021; SE=0.0037; p=0.58) (Figure 11). None of the factors considered in the meta-regression (mean age, mean educational attainment and maximum follow-up period) changed this conclusion. The findings remained stable in our sensitivity analyses, despite the high heterogeneity of the studies.

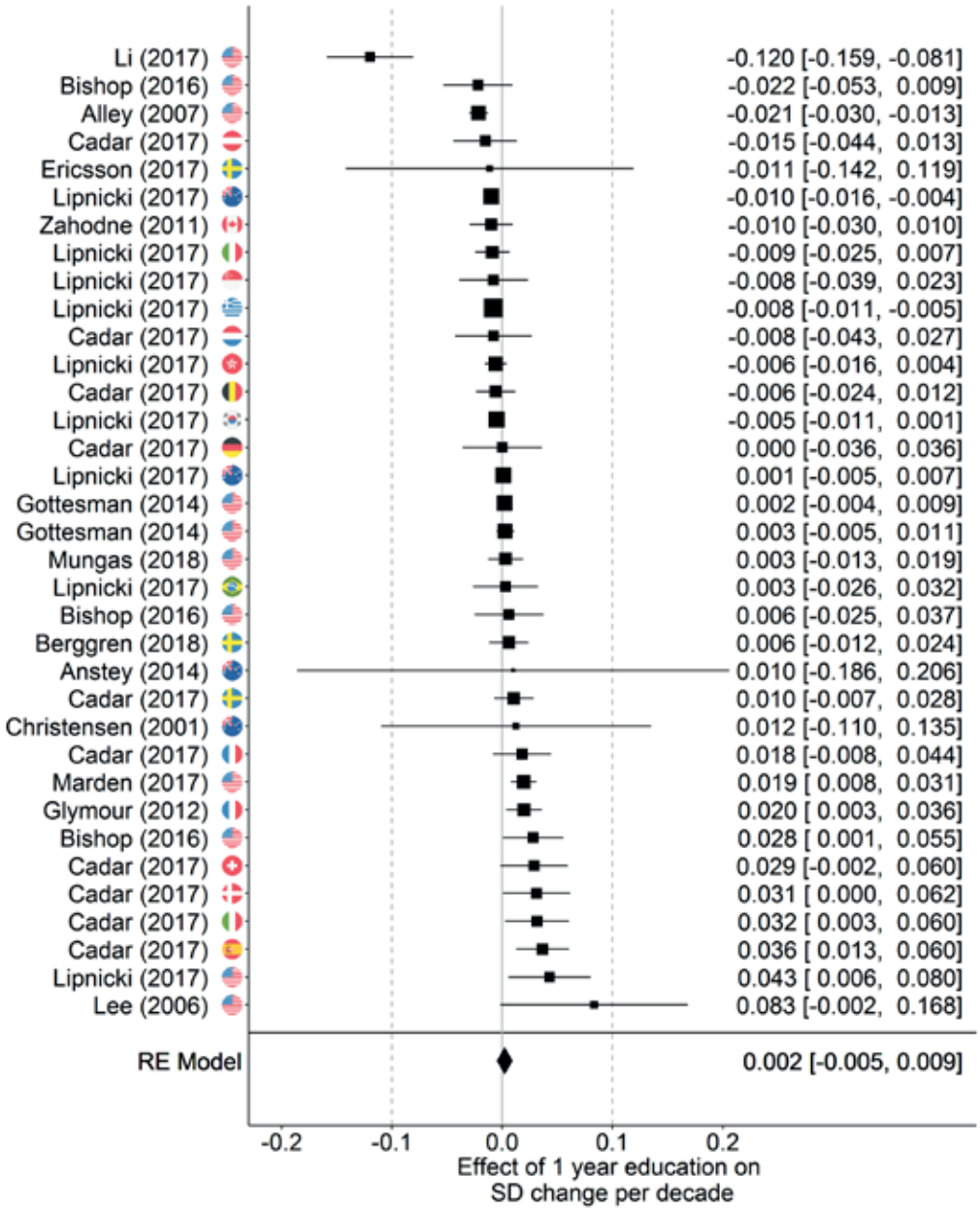


Figure 11. Forest plot of individual and meta-analytic estimates assessing the relationship between an additional year of education and change in episodic memory (in SD) per decade. Point estimates and 95% confidence intervals are provided. Size of point estimates corresponds to their weight in the meta-analysis.

5 DISCUSSION

5.1 MAIN FINDINGS

The main findings in relation to the thesis' specific aims are the following:

1. The burden of dementia in Swedish inpatient records was associated with educational level. In general, those with the highest education had the lowest dementia incidence rates.

2. During thirty years (1987-2016), the educational inequalities in dementia incidence remained relatively stable.

3. The Swedish comprehensive school reform, which prolonged education, increased intelligence during late adolesence.

4. Swedish comprehensive school reform's effect differed by socio-economic background. Those with the lowest childhood SEP gained the most.

5. Longer education caused by the Swedish primary schooling reform did not have any substantial effects on the risk of receiving dementia diagnosis in old-age.

6. The meta-analytic estimate from longitudinal studies of healthy adults indicated that the association between education and age-related change in episodic memory is negligible.

5.2 VALIDITY AND HIERARCHY OF EVIDENCE

The main findings outlined above should be evaluated in relation to the strengths and limitations of the individual studies. These are discussed in the original articles in more detail. This section focuses on several overarching methodological concerns in epidemiological research focusing on education, cognition and dementia. Further, we discuss the relationship between hierarchy and quality of evidence, especially in relation to causal inference – within and between studies. The section summarizes some key issues using examples, but it does not provide an exhaustive summary of the current debates.

5.2.1 Validity and causal statements within studies

Internal validity is commonly equated with study design (Murad et al 2016). Yet, there are many threats to internal validity, which can undermine our ability to make causal statements (Shadish, Cook & Campbell 2002) *within individual studies*. One serious threat to internal validity is *reverse causation* – a possibility that a causal relationship between an exposure and outcome actually goes in the other direction than hypothesized. Uncertainty about the direction of the link between the exposure and outcome strongly undermines our ability to interpret the findings as causal. The risk of reverse causation is the highest in

cross-sectional studies due to ambiguity of the temporal sequence between the studied factors. Yet, sometimes even in cross-sectional studies, the temporal sequence between exposure and outcome is clear. For example, a cross-sectional study looking at the relationship between education and dementia has a clear temporal sequence. Formal education is usually completed prior to 30 years of age, and thus precedes dementia diagnosis in time. Yet, educational attainment may be susceptible to other health states, for example chronic health issues in childhood that may negatively impact length of schooling (Glymour, Avendano, & Kawachi 2014). Thus, depending on the studied outcome, reverse causation between education and health still may play a role.

Another important threat to internal validity is *confounding*. Due to lack of randomization, findings in observational studies are more likely to be affected by confounding than findings from RCTs. Sometimes data on known confounding factors is not available. For example, in our *Study I* we included several confounders based on our knowledge of the Swedish healthcare system. Nevertheless, data on some factors were not available for the entire follow-up and thus could not be included in the final study. One such factor is a length of hospitalization, which may affect the likelihood of receiving a dementia diagnosis. Increasingly, Swedish clinicians face time-pressures in delivering treatment (Edvardsson, Arnholdt-Olsson & Jeppsson 2014). Therefore, they may be less likely to include detailed data on secondary diagnoses, including dementia. When data is missing possible confounding may be assessed by alternative means. For example, we looked at the overall trends in main and secondary diagnoses separately, which did not alter the overall conclusions. At other times, confounders are unknown as in our examination of the association between education and dementia in various Swedish registers presented in section 3.1.1.

One key issue undermining validity of epidemiological research on dementia is *misclassification*. Assessing the level of misclassification with regards to dementia diagnosis is complicated by the lack of golden standard for dementia (Weuve et al 2015). In this thesis, we used dementia diagnoses obtained from Swedish registers as the outcome (*Study I & Study III*). As outlined in section 3.1.1., validity studies that used diagnosis from population-based cohorts as the gold standard report low-to-moderate sensitivity of dementia diagnoses in these registers (Jin et al 2004; Rizzuto et al 2018). Therefore, many individuals that do have dementia diagnosis, are not coded as dementia cases if the registers are used. Subsequently, the studied relationship between education and dementia may be underestimated

If the misclassification is differential the studied relationship is biased, because differential misclassification introduces an association between the exposure and outcome due to other reasons than the relationships we are studying. The direction and magnitude of the subsequent bias depends on the pattern of misclassification. To the best of our knowledge, no study has reported misclassification of dementia diagnoses

in Swedish registers by educational level. Education-stratified sensitivity figures, that we obtained for the purpose of *Study III*, indicated 73.9% sensitivity (95% CI: 64.7-81.8%) for those with less than eight years of education and 68.2% sensitivity (95% CI: 55.6-79.1%) for those with at least eight years or more. The overlapping confidence intervals suggest no substantial differential misclassification and relatively low statistical power in this analysis.

Several international studies examined the validity of dementia diagnoses in healthcare databases (Solomon et al 2014; Taylor Jr, Fillenbaum, Ezell 2002; Taylor Jr et al 2009, Østbye et al 2008). Some of those studies also investigated the validity of dementia diagnoses in relation to education. Østbye et al (2008) reported that those with lower education were less likely to have a dementia diagnosis in two or more sources, when comparing data from Medicare claims, death certificates, and the Assets and Health Dynamics Among the Oldest Old (AHEAD) study (2008). One study, which compared Medicare claims, and the Aging Demographics and Memory Study (ADAMS) found that 2/3 of false negatives were individuals with low education (Taylor Jr et al 2009). Thus, those with low education were less likely to have dementia in their medical claims, even in the presence of the condition.

We also observed educational differences in receiving a dementia diagnosis when describing the overlap of the four Swedish registers (section 3.1.1.). For example, those with university education were 1.4 times more likely to be diagnosed as a case in all four registers than those with elementary education only. And those with elementary education were most likely to appear as a case only in one data source. Thus, it is possible that even in Sweden those with low education are less likely to be assigned a dementia diagnosis in the healthcare databases. However, we do not know if these differences are large enough to substantially bias the results. Therefore, further investigation of education and other factors (e.g. severity) that may affect differential misclassification of dementia diagnosis in Swedish Registers is needed.

Another major challenge in aging research, which might undermine the validity and bias the findings, is *sample selection* (Weuve et al 2012; Weuve et al 2015). Differential attrition, enrollment and refusal to participate are of concern in longitudinal population-based studies, such as those that were included in our systematic review and meta-analysis (*Study IV*). Among the studies included in the meta-analysis many did not report on enrollment proportions. Further attrition over time was varied among the studies, ranging from 11.7% to 76.0%. Attrition is expected to be higher during longer follow-up. Drop-out was 38.0% (SD 21.5) during the average follow-up of 6.54 years (SD 4.3). However, this figure included attrition due to death, refusal to participate and failure to follow-up. Each of these processes may be differentially associated with education and/or cognition. For example, Kelfve (2015) reported that demographic variables (sex, cohort, age) were stronger predictors of selective mortality, while socioeconomic factors were stronger predictors of survey participation.

Further, differential participation can lead to underestimations of the relative and absolute educational inequalities in old-age health (Kelfve 2017).

The quality of synthesized evidence is dependent on the quality of the included studies. The studies included in our meta-analysis dealt with selection issues in diverse ways, for example by modeling determinants of selection or by employing inverse probability weighting. While there are multiple techniques to address attrition due to drop-out, there is no clear consensus on dealing with *selective survival* (Weuve, et al, 2015). Yet, survival is associated with both of our main factors of interest - education and cognition. However, a question is to what extent one needs to be concerned about selective survival in studies, which include almost the total population. Population composition in such studies reflects the real-world mortality patterns of the target population. Nevertheless, for many of the subjects who die during the follow-up, the outcome remains unknown due to misclassification of dementia on death certificates. This may bias the results. Ultimately, with regards to choosing how to deal with selective survival, the scientific question examined is the key concern (Weuve, et al, 2015). For example, scrutinizing selective survival may be less important in *Study I*, where the aim was to describe the real-world situation in the target population than in *Study II* or *Study III*, which aim to inform about causal relationships.

An important ongoing discussion in the field of epidemiology focuses on the elevation of causal studies as the *science of epidemiology* (Ebrahim, Ferrie & Davey Smith 2016). One point in the debate is elevation of study designs, such as RCTs, and methodologies, as the restricted potential outcomes approach, above all others. We believe that the debate has been muddied by the lack of distinction between *making causal statements* within individual studies and *arriving at causal conclusions*. If executed appropriately some study designs or methodologies indeed allow for making causal statements with higher certainty because they deal better with the threats to validity described above. Yet, as Blakely, Lynch and Beteley, pointed out there is a difference between tools and theories of causation (2016). Many philosophical theories of causation have been developed. However, what we believe is key for epidemiology is the use of different kinds of evidence in order to arrive at causal conclusion. We maintain that causal conclusions are made across studies; and thus synthesis of evidence is of key concern.

5.2.2 Synthesis of evidence and arriving at causal conclusions

Multiple heuristics for evaluating and summarizing evidence exist. Synthesizing evidence is key for *arriving at causal conclusions* because if findings are observed across diverse contexts it strengthens the reliability of the conclusion.

One example of heuristic is the evidence pyramid, which became increasingly common after the 1990s due to the rise of evidence-based medicine (Shaneyfelt 2016). However, other heuristic models exist, for example the Grading of

Recommendations Assessment, Development and Evaluation (GRADE) model or the Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence (Howick et al 2011) model. All of these heuristics have been modified over time to better portray the complexities of available evidence and the rising number of information resources (Alper & Haynes 2016; Murad et al 2016, Howick et al 2011). Even if diverse metrics are used to assess the hierarchy of evidence, the main idea is always the same – evidence with higher risk of bias is placed at the bottom and trusted less. However, evidence ranking is to a certain degree subjective and we believe that many questions concerning the quality and hierarchy of evidence regarding the relationship between education and dementia remain. In what follows, we discuss some of these issues.

Early versions of the heuristic models categorically placed RCTs as a central method for obtaining high quality evidence. Subsequently, summaries of RCTs were at the top of the evidence hierarchy (Howick et al 2011). Yet, many have pointed out that poorly executed RCTs or ones funded by private organizations may also be subject to substantial bias (Howick et al 2011). Further, some questions cannot be studied in the RCT framework (Smith & Pell 2003). As discussed in the introduction, education is one such exposure. Quasi- and natural experimental studies, as our *Study II* and *III* build on the concept of pseudo-randomization, and are an alternative to RCTs. As such, synthesis of evidence from quasi- and natural experiments is becoming more popular (e.g. Hamad et al 2018). However, it is important to assess the success of pseudo-randomization since it is unlikely to hold for all such studies. An incorrect analysis can also lead to loss of pseudo-randomization. Quasi- and natural experimental studies also have other weaknesses, such as limited range of exposures, and wide confidence intervals since only certain proportion of the population is affected (Kubzansky, Seeman & Glymour 2014, p.523).

Evaluating the quality and possible hierarchy of evidence in dementia research is hampered by the lack of a gold standard for dementia diagnosis (Weuve et al, 2015). As outlined in section 1.3.1., many different methods for ascertaining dementia diagnoses are adopted in research settings. Further, various procedures may be differentially sensitive in specific sub-populations, such as low education groups, or ethnic/racial minorities. This in turn may impact estimation of inequalities in dementia. Thus, the question of how to best evaluate the strength of evidence from cohort studies in dementia research remains. For example, should population-based cohort studies be seen as superior to register-based ones? The use of diagnoses from population-based studies as the gold standard indeed suggests that they are the preferred choice. We would like to warn against this generalization since certain questions, for example the one addressed in our *Study I*, cannot be answered in population-based setting.

In summary, we believe that in order to *arrive at a causal conclusions* plurality of evidence should be considered

and the value of evidence should not mechanically be assessed based on a pre-defined hierarchy of study designs or other simplistic methods. After all, the heuristic models "are general guides about the quality of evidence, not rules" and these guides should be used mainly "at the point of care where time is more limited" (Shaneyfelt 2016, p.121) or in teaching. When evaluating and synthesizing research, there are no shortcuts to detailed consideration. Overall, knowledge claims, especially causal ones, should be evaluated with regards to methodological concerns, the overall aims, their role in relation to the entirety of available evidence and to ruling out alternative explanations.

5.3 FINDINGS IN CONTEXT OF CURRENT RESEARCH

Each of the individual studies in this thesis adds another piece of the puzzle in the whole of available evidence regarding the relationship between education, cognition and dementia. Therefore, it is necessary to set the findings in context for possibly arriving at causal conclusions.

In *Study I* we described trends in the burden of dementia using Swedish inpatient records and found stability of educational inequalities (both relative and absolute) in dementia incidence during thirty years. While there is a number of studies examining dementia incidence using healthcare data (Table 8), none of them considered education as a factor. The results from population-based studies, revealed mixed evidence. Satizabal et al (2016) did not find any association between education and trends in dementia incidence. On the other hand, according to Grasset et al (2016) higher education was associated with an observed decline in dementia incidence.

There are likely substantial differences between studies using healthcare data and those using data from population-based studies. Receiving dementia diagnosis in healthcare databases, might suggest more severe impairments than receiving dementia diagnosis in population-based studies, since they tend to include more healthy individuals. Participation and attrition in population-based studies is also associated with socioeconomic factors, such as education, and highly educated individuals are more likely to remain during the follow-up (Kelfve 2015). These differences may partly explain the observed discrepancies in findings. However, the evidence remains sparse.

Our *Study I* finding of a decreased burden of dementia in Swedish hospitals during the last half a decade was in line with a recent narrative review. The summarized evidence indicated declining or stable trends (Wu et al. 2017). According Wu et al (2017), studies like ours, which are based on insurance databases, medical or healthcare records, are classified as secondary evidence due to their susceptibility to changes in medical practices, public awareness and other factors. There are seven published studies using healthcare data and they covered diverse geographical regions and periods (Table 8). Four out of the seven studies reported

increasing dementia incidence, whereas three reported the opposite (including Seblova et al. 2018). However, the study by Seblova et al. (2018) found a decrease only after 2010. On the other hand, four out of six dementia incidence estimates from population-based cohort studies found stable incidence rates over time. Two reported a decline in dementia incidence (Table 8). Differences in study sample composition may also influence the findings regarding the overall trends. Highly educated individuals tend to adopt health advice earlier, and thus effects of smoking reduction, improved cardiovascular health or other risk/protective factors might be observed earlier in the population-based cohorts. Out of the four healthcare data studies with follow-up in the second decade of the 20th century, three reported decline in dementia incidence (Table 8).

Table 8. Summary of studies using healthcare data or community cohorts and reporting on the dementia incidence trends.

Study	Geographical Region	Follow-up period	Dementia incidence
Healthcare data studies			
van Bussel et al. (2017)	Neatherlands	1995-2017	↑
Abdulrahman (2014)	United Kingdom (Wales)	1999-2010	↑
Ukraintseva et al. (2006)	USA	1984-2001	↑
Chien et al. (2008)	Thaiwan	1996-2003	↑
Sposato et al. (2015)	Ontario, Canada	2002-2013	↓
Kosteniuk et al. (2016)	Saskatchewan, Canada	2005-2013	↓
Seblova et al. (2018)	Sweden	1985-2016	↓
Community population-based cohort studies			
Schrijvers et al. (2012)	Neatherlands	1990-2000	↔
Grasset et al. (2016)*	France	1980-1999	↔
Matthews et al. (2016)	United Kingdom	1991-2008	↔
Gao et al. (2016)	USA	1992-2001	↓
Gao et al. (2016)	Nigeria	1992-2002	↔
Satizabal et al (2016)	USA	1977/83-2004/08	↓

*Grasset reported clinical (reported in table) and algorithmic diagnosis (not reported), which showed a decline in dementia incidence.

The findings of *Study II* were in line with previous research that indicated a causal effect of education on intelligence (Ceci, 1991; Brinch & Galloway, 2012; Carlsson et al 2012; Ceci 1991; Cliffordson & Gustafsson 2001). The study had two unique contributions – an examination of effect heterogeneity according to childhood SEP and a focus on adolescence. The malleability of cognitive abilities is thought to be greatest in early childhood (Heckman 2006). However, the findings in *Study II* suggested that prolonged education in early adolescence is also beneficial for intelligence. Our ability to determine the exact timing of the effect was another of the study's strength. Some studies (e.g. Glymour et al. 2008) employed changes brought about by several laws altering education starting age, legal drop-out age or work-permit age. Subsequently, the timing of the effect was unclear.

Examination of heterogeneity of causal effects has been highlighted as an important avenue for future research of compulsory schooling reforms (Glymour & Manly 2018). Yet, many quasi-experimental studies are unable to do this due to limited statistical power. In our large register-based study, we found that the comprehensive school reform, which introduced an extra year of schooling, reduced inequalities in intelligence according to childhood SEP. Likely, this was the key findings of the study. Those from lowest socioeconomic backgrounds benefited the most from the reform, while intelligence of those from the highest socioeconomic backgrounds was not substantially affected.

A major contribution of *Study III* was the examination of the causal effect of education on actual dementia diagnosis in a large sample. Evidence regarding this topic comes predominantly from Mendelian randomization studies, which used genetic correlates (genome-wide associations) to identify AD dementia as an outcome (Table 9). Three out of the four studies were based on the same data from the International Genomics of Alzheimer's Project (Lambert et al 2013). Varied single-nucleotide polymorphisms (SNPs) were used as an instrumental variable for education in the Mendelian randomization studies. One studies used only one SNP, while another one used 152 SNPs. The findings have been mixed, and estimates were imprecise, as indicated by the wide confidence intervals (Table 9). Studies that used the highest number of SNPs reported the largest reductions in the risk of Alzheimer's disease. However, using many SNPs still captures only small (0.06%) variation in years of education (Anderson et al 2017). Furthermore, the SNPs for educational attainment are likely associated with early-life cognitive ability, which would violate the fundamental assumptions of this method. Finally, the Mendelian randomization studies were limited to one subtype of dementia.

As discussed in the introduction, education is a bundled process and so are educational reforms. Subsequently, identifying specific mechanisms of action is problematic. *Study II* suffered from this weakness. On the other hand, in *Study III* we were able to eliminate many potential mechanisms due to the limited spillover effects to adult socioeconomic factors and the uncomplicated nature of the reform. We found that prolonged education brought about by the Swedish primary schooling reform did not have any

substantial effects on the risk of receiving a dementia diagnosis in old-age (Table 9). One previous study that used many compulsory schooling law changes as the exposure, found a protective causal effect of education on a dementia probability risk score (Nguyen et al 2016) (Table 9). However, isolating the exact mechanisms was impossible due to the mixed nature of the exposure. While the evidence on causal effect of education on dementia remains to be corroborated, our study is a step forward in this endeavor.

Finally, our systematic review and meta-analysis (*Study IV*) adds to the discussion regarding the association of education with age-related cognitive change by synthesizing the current evidence from population-based studies. We focused on episodic memory - a cognitive domain with strong links to dementia (Bäckman et al 2005). In older age episodic memory declines on average with 0.4-0.5 SD per decade. Based on 35 estimates and 92,930 subjects we found a negligible association between education and change in episodic memory (β = 0.0021, 95% CI = -0.005 – 0.009, p = .58). As presented in the introduction, three previous summaries have been conducted and reported mixed evidence (Anstey & Christensen 2000; Lenehan et al 2014; Valenzuela & Sachdev 2006). However, our results agreed with the most recent findings (Lenehan et al 2014). Further, our study also identified substantial heterogeneity across the studies. It is possible that in different contexts (e.g. societies, time-periods, etc.) education is heterogeneously associated with change in cognitive performance. However, we were unable to explain the observed heterogeneity and thus this remains a subject for future research.

5.4 IMPLICATIONS AND FUTURE RESEARCH

Monitoring trends in dementia in diverse settings is important not only from a research perspective, but also from a resource planning one. Our *Study I* suggested an improvement in public health since the number of new patients with dementia diagnosis in Swedish hospitals seemed to be decreasing in the last half a decade. However, how this may influence the burden of dementia cases presenting in other healthcare sectors, for example primary care, remains to be examined. The trend is parallel for individuals with different levels of educational attainment. This means that inequalities in dementia incidence remained stable, which can be considered a positive development. Yet, further examination of education's role is another avenue for future research since relatively few studies have focused on it. One clear limitation is that our study was not suitable for estimating current and future dementia incidence in the whole of Sweden. Subsequently, population-based studies, including institutionalized individuals, are needed.

The Swedish Commission for Health Equity stated that "strategies for fostering good and equitable health should include an opportunity for everyone to develop their skills and knowledge, and acquire education" (Lundberg 2017, p.7). The results from *Study II* indicated that changes in the educational system can indeed bring about reduction of inequalities, in this case in intelligence, which in turn predicts mortality and other health outcomes. Future research should examine if education has different effect

on outcomes in socioeconomically diverse groups, in men/women or groups divided by another factor. Furthermore, the evidence on the mechanisms underlying this effect needs to be expanded.

Table 9. Summary of studies examining causal effects of education on dementia using either Mendelian randomization or compulsory schooling reforms as instruments for educational achievement.

Study	Sample	Measure of demetnia	Measure of variation in education	Results
Mendelian Randomization studies				
Østergaard et al. (2015)	n=54,162 Multicountry: samples of European ancestry	GWAS of Alheimer's disease patinets from International Genomics of Alzheimer's Project	1 SNP (rs12206087) Scale: years of education	OR= 0.71 95% CI: 0.48 to 1.06
			2 SNPs (rs11584700 & rs4851266) Scale: probability university completion	OR=0.95 95% CI: 0.67 to 1.34
Nguyen et al. (2016)	n=7,981 USA: Caucasian sample only	Dementia probability score (range 0-1); 94.3% prediction of DMS-IV diagnosed dementia	Genetic risk score based on 3 SNPs (rs11584700; rs4851266; rs9320913) Scale: years of education	β(IV)= -0.011 95% CI: -0.024 to -0.002
Larsson et al. (2017)	n=54,162 Multicountry: samples of European ancestry	GWAS Alheimer's disease patinets from International Genomics of Alzheimer's Project	152 SNPs Scale: years of education	OR=0.89 95% CI 0.84 to 0.93
			32 SNPs Scale: probability university completion	OR=0.74 95% CI 0.63 to 0.86
Andersson et al. (2017)*	n=54,162 Multicountry: samples of European ancestry	GWAS Alheimer's disease patinets from International Genomics of Alzheimer's Project	63 SNPs Scale: years of education	OR=0.63 95% CI: 0.48 to 0.83
Compulsory schooling refom studies				
Mazzumder** (2008)	n=17,993	Self-reported senility/ dementia/Alheimer's disease in subset of study participants (those with work limitation)	42 compulsory school laws combinations Scale: years of education	β(IV)= -0.0015 SE 0.0006
Nguyen et al. (2016)	n=10,955 USA: excluding those with >12 years education	Dementia probability score (range 0-1); 94.3% prediction of DMS-IV diagnosed dementia	42 compulsory school laws combinations Scale: years of education	β(IV)= -0.095 95% CI: -0.148 to -0.042
Seblova et al. (Study III)	n=1,341,842 Sweden: nearly total Swedish born population (exclusing immigrants)	Dementia diagnosis in National Inpatient or Cause of Death Registers	1 primary schooling reform Scale: years of education	HR=1.01 95% CI: 0.98 to 1.04

*Pre-print; **Note: High risk of selection bias in the study. Further, suspected low quality of dementia diagnosis, especially for severere dementia due to self-report. Interpretation as effect on old-age cognition or decline of thereof is more appropriate. GWAS= Genome-wide association study; SNP= Single nucleotide polymorphism; OR= Odds ratio; CI= Confidence interval, IV=Instrumental variable; HR= Hazard ratio; DSM= Diagnostic and Statistical Manual of Mental Disorders.

Findings of our *Study III* brought into question whether longer education can reduce dementia incidence. We did not find any direct causal effect of prolonged education on old-age dementia. However, our studied exposure (prolonged education due to primary schooling reform) did not affect mid- and late-life socioeconomic conditions. If our finding stands up to scrutiny and replicates in future studies, life-course models linking education and dementia need to be updated (Liu, Jones & Glymour 2010). According to our findings, chain of risk model, where prolonged early life education needs to affect subsequent processes (e.g., adult cognitive engagement) that in turn affect the risk of dementia, seemed to be a key mechanism. This would correspond to the indirect pathways presented in Figure 1. All in all, more studies, especially those exploiting quasi-experimental designs, are needed to shed light on the nature of the relationship between education and dementia.

Finally, our systematic review and meta-analysis (*Study IV*) called for a reexamination and revision of the theories of cognitive aging in healthy adults, since education's association with age-related change in episodic memory was negligible. However, individual cognitive processes have specific patterns of decline (Rönnlund & Nilsson 2006; Schaie 1994, 2005). Thus, future summary of evidence regarding the association between education and decline should be expanded to include other domains.

5.5 FINAL REMARKS

This thesis posed both descriptive and causal questions regarding the links between education, cognition and dementia. In seeking the answers diverse designs were employed. Combining previous evidence, and findings presented in this thesis, it remains unclear if and by what mechanisms education might reduce the risk of old-age dementia. Our findings indicated that early-life education needs to be followed by a change in adulthood socioeconomic position and/or cognitive stimulation in order to have an effect on dementia. Decline in episodic memory, a cognitive domain with strong links to dementia, was also not associated with education. This suggests that a true protective effect (if any) may be mediated by increasing the level of cognition, rather than slowing cognitive decline. Because of increasing burden of dementia, its subsequent consequences and costs, there are important societal implications to the finding that education might not have the potential to reduce dementia incidence. Nevertheless, improving health has never been the main aim of education.

One of the key goals of education is to improve individual's abilities in order to ready them for the future. Based on the evidence presented in this thesis, we concluded that there is convincing evidence of a causal effect of education on early and old-age cognition. Another goal of education is to promote equal opportunities. We found that even in this aspect education may be able to fulfil societal aspirations by for example reducing socioeconomic inequalities in intelligence. Thus, education without a doubt remains an important pillar of our societies.

6 ACKNOWLEDGEMENTS

Recall bias is a well-known epidemiological phenomenon. For a long time, I had nightmares about a specific type of this bias - acknowledgement recall bias! If you are a subject to this bias, I apologize and please know that it will haunt me for a long time!

It is impossible to not recall my **supervisors**, who have guided me through this formidable endeavor of obtaining a PhD, even when life heavily intervened with death, sickness, and injuries. First and foremost, I am grateful to my main supervisor Anton Lager - thank you for choosing me as your first ever PhD student, for your advice when the way forward was unclear, for sharing your creative scientific mind, and Swedish way of life. I would also like to thank my co-supervisors – Martin Lövdén, Anna Christina Svensson, Stefan Fors, and Kristina Johnell, who have been integral to this journey. Thank you, Martin, for taking charge in critical moments in a calm and reflective manner. Many times, you were a lighthouse to navigate by. Anna, you have always reminded me why I love research and discussed it passionately with me (while nourishing me with excellent dinners) – thank you for that! Stefan and Kristina, you have my deepest gratitude for your diplomatic guidance, prompt feedback, and longstanding support.

Wholehearted thanks also go to my official **mentor** Ylva Brännström Almquist. Thank you for not being scared of tears. All of my **co-authors** (Daniel Falkstedt, Martin Karlsson, Therese Nilsson, Antonio Ponce de Leon, and Rasmus Berggren) have also been mentors by making me think harder and research better. Special thanks to Susanne Wicks, who taught me all I know about management of millions of observations and hundreds of variables from Swedish register data. Maria Lopez Quiroga, my first mentee and co-author, thank you for helping me figure out the first steps in my path as a mentor. Martin Fischer, you were my favourite collaborator from early on, and I am so glad we also became friends. Thanks for respecting me no matter what, being there for me, and re-introducing me to my hometown– děkuji! Kimberly Kane, your editing made my manuscripts better and our anthropological theory chats reminded me where I come from.

As causal conclusions are made between studies, my PhD was conducted in between departments and research groups – I spent time at the Aging Research Center (ARC), at Department of Public Health Sciences (PHS) and at Centre for Epidemiology and Community Medicine (CES). Many individuals from these institutions encouraged me.

Therefore, my gratitude goes to my current and past **colleagues from ARC** especially: Johan Fritzell, Laura Fratiglioni, Lars Bäckman, Anna Marseglia (for her advice and volleyball games), Linnea Sjöberg (for being kind and supportive), Alexander Darin Mattson (for letting me rant during our Byn lunches), Charlotta Nilsen (for heart to heart talks), Bárbara Avelar

Pereira (for cheering me on), Cristina Dintica (for not getting too scared of me by our first encounter), Jonna Nilsson Horré (for encougarement), Ylva Koehncke, Alexander Lebedev, Malin Ericsson, Ingemar "Pingo" Kåreholt (for lightening up the mood), Neda Agahi (for her support), Stina Ek, Mozhu Ding, Behnaz Shakersain, George Samrani, Debora Rizzuto (for dementia sensitivity estimates), Giola Santoni, Anna-Karin Welmer, Nicola Payton, Edwin Tan, Miriam Haaksma, Serhiy Dekhtyar, Claudio Brozzoli, Janina Seubert, Johan Rehnberg, Louise Sundberg, Rui Wang, Lieke de Boer, Greg Kalpouzos, Xu Weili, Hui-Xin Wang, Calderón-Larrañaga, Amaia, and all others.

My warm thanks also extends to past and present **members of EPiCSS research group** at PHS - especially to Christina Dalman (for providing a research home base), Renee Gardner (for endless encouragement and obi-ban videos!), Sofia Löfving (for her open heart), Maria Niemi and Rynaz Rabiee (for sharing office with me), Alma Söderberg Wallin (for listening and reassuring), Jill Witney Åhs and her wonderful kids Eva and Ari (who lightened up so many of my days and decorated my crutches), Hélio Manhica (for hugs and advice from few steps ahead), Henrik Dal, Sara Sjölund, Lovisa Sydén, Andreas Lundin, Kyriaki Kosidou, Anna-Clara Hollander, Edison-Manrique-Garcia, and others.

Many thanks also to the **members of PRIME Health research group** at PHS – Nora Döring (for her friendship and encougarament), Cecilia Magnusson, Michael Wells (the best open-office neighbor), Sofie Possmark, Fanny Sellberg, Emelie Thern, Isidora Stark, Daniel Berglind, Michael Lundberg and Peeter Fredlund (for sorting out my SAS questions), Lene Lindberg, Per Tynelius, Regina Winzer, Selma Idring, Maki Morinaga, Nuhamin Petros, and all others.

Support and encouragement also poured from colleagues from Unit for Health Status and Care Needs Analysis and other **CES employees**. Thank you among others - Joanna Stjernschantz-Forsberg (for comforting me during our fikas), Emelie Andersson, Charlotte Jansson (for sharing your outdoors equipment), Frida Lindh, Sofie Jonsson (my Swedish half-classic buddy), Fredric Ripe, Peter Guban (my patient office-mate), Vicky Bartelink, David Ebbevi, Marie Warolén, Diego Yacaman Mendez, and Joseph Muwange Jr.

Thanks to also all other **Widerstömska and Torsplan officemates** for lunch and fika company – Stephan Lawoko, Alessio Crippa, Diana Corman, Megan Doheny, Melody Almroth, Katalin Gémes (also for climbing breaks!), Ari Willy Duggal (a kind roommate in rocky times), Devy Elling (for our knee-rants), Malin Ulfsdotter, Linda Shala, Dang Wei, Venus Hailemichel, Therese Wirback, Lisa Harber-Aschan, Madelene Barboza, and Yajun Liang (for so many hugs).

None of our research would be possible without the outstanding support we get from our **administrators**. My gratitude goes especially to Vanessa Suthat, Maria Yohuang, Maria Wahlberg, Cecilia Annerholm, Christian Lynghaug, Johanna Bylund, Ewa Anderson, Malin Pettersson, and Marie Helsing-Västfjäl.

I would like to thank **my teachers and classmates from the Swedish Interdisciplinary Graduate School in Register-based Research (SINGS)**, especially - Anita Berglund, Gustaf Brander (for our online check-ins), Can Liu (for lovely lunch company), Mwenya Mubanga (for all the laughter and sincere life talks), Natalie Holowko (for our Hemköp fikas/lunches), Olof Östergren, Kathrin Morosow, Sara Kalucza, Siddartha Aradhya and Hanna Mogensen. I have witnessed my first Northern Lights in your company, while studying causal inference, and it was truly unforgettable! I would also like to express my thanks to the **MELODEM group**, especially Maria Glymour and Elizabeth Rose Mayeda, for reinvigorating my nerdy side. To the **PhD Career Research Blog** team for making me a better writer, and the **PhD Career Podcast Stories** team for showing me that teamwork can function.

These past five years have been one of the hardest in my life. I was forced to get to know myself better and explore the limits of my resilience. I mostly just crawled through (or hopped on crutches while learning to walk again). I am grateful to all those who stepped in times of need. My sincere thanks to the Previa healthcare staff, and especially my psychologist Emmy Lindedal. Thanks also to all the animals (and their owners), who calmed me - Henry (and Heather, in that order), Alan, Samik, Dita, and Lilly.

There are no words to express how thankful I am to **my friends and family**, you have walked by me, no matter my speed or mood, you had faith in me when I lost it. I am grateful and here because of you. Thank you, Karin, for being with me in many (natural and life) storms, in harsh weather such as -17 °C tents sleep-overs and making it all enjoyable. You make life an adventure. Marie, my hundred-percent soul-sister, thank you for picking me up in middle of snowstorms (mental or actual) and taking me out for pancakes (or otherwise comforting me). Martina thank you for being YOU! And for always reminding me that I am worth the way I am. Emerald, thank for being my anchor point, softening my falls with your belay skills, open-heart and ears. Jen, my Canadian adventure soulmate, thank you for making office hallways ring with laughter, encouraging my mischievous ideas (like shaving my head and going above the polar circle) and for making me feel like I not alone when I most needed it. Thank you, Linnea, for our wonderful road trip, endless chats, and your homemade ice cream! Maria, you are my life-role model, I want to be as amazing as you one day and cycle Tjejvättern! Thank you for your open heart and wisdom. Cecilia, I am grateful for your warm-heart, our mushroom picking, and for being able to be honest about life-hardships. You are an inspiration to me!

To my Czech crew – Gabriela, Pavla, and Lenka – for our cultural confusion rants over some proper beer. My Settlers frenemies - Samuel and Erik – for the long boardgame nights. Nicholas, my UWC “classmate” for being there when walking was a hard task. Bogo – for the coffee maker, dinners, and your San Francisco apartment! Ahmed, for helping out and checking on me. Eva, for your overall awesomeness. My thanks also go to Kevin, Núria, Els, Arzu, Chenhong, Mikaela, and the Meepo

boys (especially Sebastian, Henrik, and Anders) for providing a work-refuge for me. My Andra Chansen volleyball team, especially Angela, Laura, Claire, Simon, Jonas, and Michael – for laughing with and sometimes at me.

I am eternally grateful for friends, who could not be stopped by oceans or national borders while supporting me – Hannah and Katy – for always being there for me. Honza – for being my home, no matter where in the world we meet. Lisa – for pretzels, postcards, and for opening your home. Bulat, for baby elephants. Vera (and Ivan) for your encouragement in the last phases. Ida – for taking me into your heart, it's an honor and privilege. Báře, za dvacet (!) let přátelství v dobrém i ve zlém.

To my family, or to be precise families. Annika, Olof, William, Ludvig, Elliot (and Svennis) – thank you for giving me my first home in Sweden. Thank you Nor, my cousin Ondra (for reuniting), to my little brother Jáchym (for coming to see my Swedish life). Tati, děkuji za guláš a péči po operaci. I am extremely grateful for my sister Nina, who has supported me, especially in the last phases of this journey. My grandmothers, who have left this world, but never my heart. Especially my grandmother Irena, who always held my hand and guided me forward. And most importantly, to my mum Jana – you made me who I am, you are an endless inspiration and my closest friend.

"It's only with the heart that one can see rightly." (Saint-Exupéry)

You all taught me how to see rightly in this pursuit of knowledge.

Nika Seblova,

30th January 2019. Stockholm.

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